THE UNIVERSITY OF ALBERTA

I. RADICAL ANION PROMOTED REDUCTION OF STERICALLY HINDERED ESTERS.

II. A STEREOSELECTIVE REDUCTION OF CYCLIC KETONES.

by

© FRANCIS JAMES CEDAR

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
FALL, 1973

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

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II. A STEREOSELECTIVE REDUCTION OF CYCLIC KETONES.

submitted by FRANCIS JAMES CEDAR in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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Supervisor

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External Examiner

Date. . . Sept 7/73 . . .

TO
THE MEMORY
OF
MY FATHER

J. J. BERZELIUS
(1779 - 1848)
Uppsala, Sweden

↓

L. GMELIN
(1788 - 1853)
Heidelberg

↓

F. WOHLER
(1800 - 1882)
Gottingen

↓

J. REMSEN
(1846 - 1927)
John Hopkins University

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E. P. KOHLER
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ABSTRACT

The reductions of three hindered esters of differing steric environments by three radical anion reagents [sodium naphthalene (NaNp), sodium hexamethylphosphoramide (NaHMPA) and sodium trimesitylboron (NaTMB)] were investigated. Reduction with sodium naphthalene gave rise to some unique alkylation products wherein coupling had occurred at the β-position of the naphthyl moiety. Alkylation products were also obtained in NaHMPA reductions. The product distribution was found to be highly dependent on the type of radical anion used, reaction time and the presence of a proton source. The order of reducing ability for these reagents was found to be NaHMPA $\gg$ NaNp $\gg$ NaTMB. Sodium trimesitylboron showed promise as a selective reducing agent.

Three new crystalline organoboranes have been prepared - dimesitylborane, lithium dimesitylborohydride, and lithium dimesitylborohydride bis(dimethoxyethane). The latter compound was shown to reduce the carbonyl function of cyclic ketones in quantitative yield, and with the highest stereoselectivity recorded for organoborohydride reducing agents. Lithium dimesitylborohydride bis(dimethoxyethane) is a unique stable complex formed between two molecules of dimethoxyethane (DME) and lithium dimesitylborohydride. Its X-ray structure is recorded.

ACKNOWLEDGEMENTS

The author wishes to thank Messrs. R. Swindlehurst and G. Bigam and their staffs for recording of the infrared and nmr spectra, Dr. A. Hogg, Mr. A. Budd, and the staff for running the mass spectra, and Mrs. D. Mahlow and Mrs. A. Dunn for determining the microanalyses. A special note of thanks is due to Mrs. M. Dawe for the typing of this manuscript.

The author is indebted to the National Research Council of Canada and the University of Alberta for funds which enabled this work to be accomplished.

Many thanks are due to the members of the lab for hours of helpful discussion and constructive criticism, in particular to Drs. L. St. Laurent and S. Akiyama with whom the author shared common areas of research.

Finally, the author wishes to express his sincere thanks to his research director, Dr. J. Hooz, for providing the encouragement and assistance necessary to develop and complete this manuscript.

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PART 1

RADICAL ANION REDUCTIONS OF STERICALLY HINDERED ESTERS

GENERAL INTRODUCTION

Radical anions[1,2,3] are negatively charged species possessing an odd number of electrons which are usually easily generated by treating a neutral molecule with an alkali metal (eq. 1).

$$AB + M \longrightarrow M^{+}[AB]^{\overset{\cdot}{-}} \qquad (1)$$

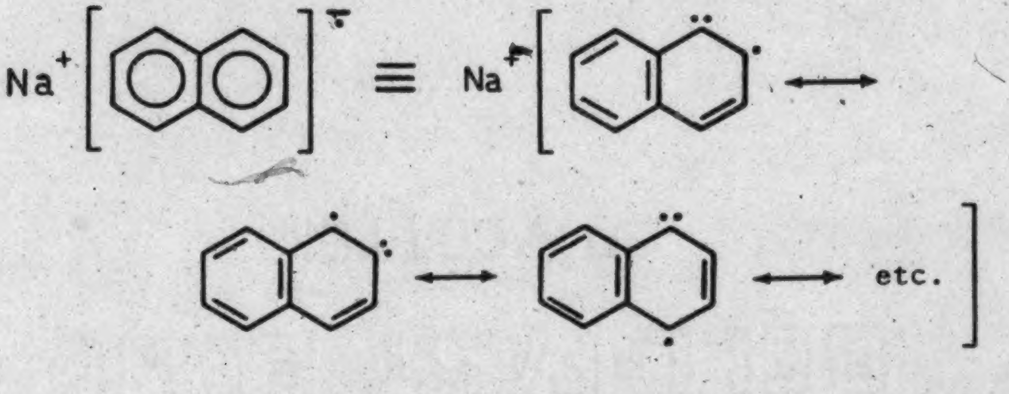
Of particular interest in the present study is the chemistry of three distinct radical anions; namely, those originating from naphthalene[4](Np), hexamethylphosphoramide[5] (HMPA) and trimesitylboron[6,7](TMB). All three radical anions are generated in a similar manner - chemical reduction with alkali metals in polar aprotic solvents such as dioxane, tetrahydrofuran(THF) or dimethoxyethane(DME). Anhydrous and oxygen-free conditions are necessary both for the generation and maintenance of solutions of stable radical anions

Historically, the radical anion of naphthalene was the first of these three to be discovered. In 1867, Berthelot[8,9] described the formation of a black addition product on fusing metallic potassium with naphthalene in a closed tube. In 1928, Schlenk and Bergmann[10] observed a reaction between lithium and naphthalene in diethyl ether, but reported no detectable reaction with sodium under similar conditions. To Schlenk is attributed the first real understanding of the nature of radical anions. Earlier work concerning the chemistry of sodium anthracene and of ketyls in ether solutions[11] led Schlenk to report his findings in terms which closely correspond to our modern notation of electron transfer processes involving carbanions, radicals and radical-ions.

A solution of sodium in liquid ammonia was the first method reported to bring about the "addition" of sodium to naphthalene in solution.[12] Then, in 1936, Scott and coworkers[4] described what has since become the most common method for its preparation; namely, in specific solvents such as dimethyl ether or DME, metallic sodium reacts with naphthalene rapidly, producing a dark green homogeneous solution. These workers also observed that addition of benzene to the green solution, followed by removal of the ethereal solvent, led to a reversal of the reaction - sodium naphthalene was reconverted into naphthalene and sodium dust.

The dark green solution of sodium naphthalene (also referred to as sodium naphthalenide) conducts electricity[4] and exhibits an electron spin resonance(esr) spectrum.[13,14]

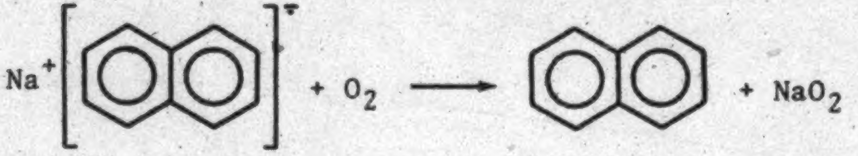
The esr signal shows hyperfine splitting due to interaction of the unpaired electron spin with the nuclear spins of the four α and four β hydrogens of naphthalene.[15] This confirms the presence of a radical anion sodium salt with the odd electron delocalized about the naphthalene molecule, thus:



Reduction thus gives a stable species which can be reconverted to naphthalene by oxidation.

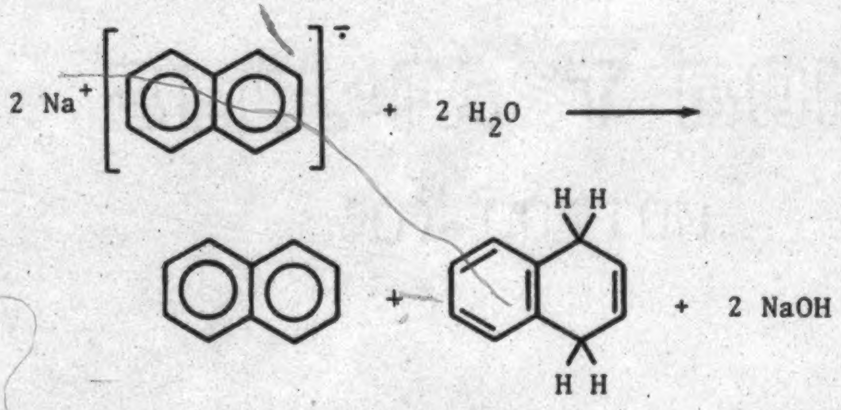
Scott[4] also noted that the reactions of sodium naphthalene could be divided into two classes. Using his terminology, the classes were: (1) those reactions in which naphthalene is recovered unchanged - such as the reactions with mercury, oxygen or benzyl chloride; and, (2) those reactions where naphthalene is reduced to dihydronaphthalene or its derivatives - citing reactions with water or organic compounds containing active hydrogens, e.g. acetylene or alcohols.

In present-day terms, the first class are called electron transfer processes as illustrated (eq. 2) for the reaction with molecular oxygen. The second, and most



(2)

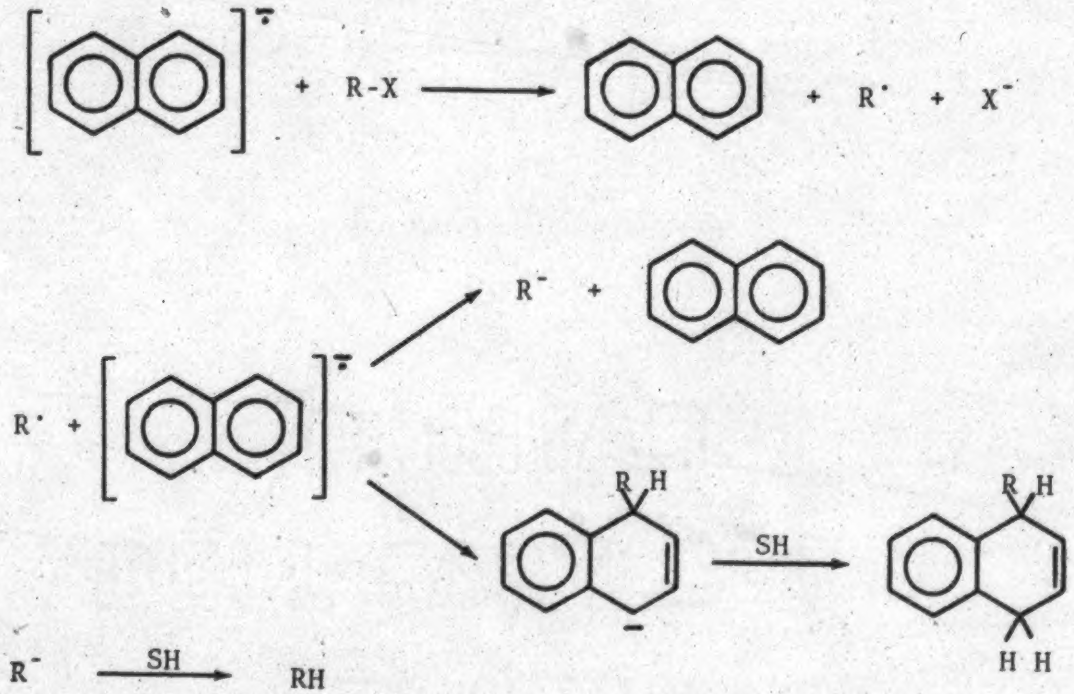
characteristic reactions of radical anions, are now termed "protonation" or "nucleophilic" reactions, i.e. the radical anions act as bases. An example is the quenching of sodium naphthalene with water[16-18] (eq. 3).



(3)

Some reactions, for example, the reduction of organic halides by the naphthalene radical ion[4,19-40] encompass both types of classes (Scheme I - the cation is omitted for convenience).

Scheme I



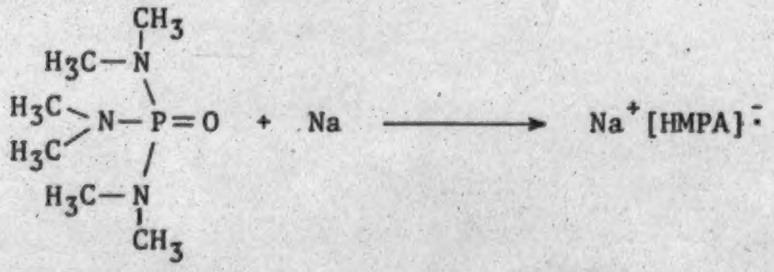
$$R^- \xrightarrow{SH} RH$$

$$R^- + R\text{-}X \longrightarrow R\text{-}R + X^-$$

This duality of reactivity of sodium naphthalene has been the subject of numerous recent studies.[17,41,42] Banks and coworkers[17,41] have suggested that the extent of electron transfer and proton abstraction are functions of the state of ion-pairing in the solvent system used. Kinetic studies have shown that for electron transfer from sodium naphthalene to naphthalene, the reactivity order is "free" > "loose" > "contact-ion" pairs[43], whereas for proton transfer to sodium naphthalene by water, the order is "contact" > "loose" > "free" ions.[17] Esr studies of sodium naphthalene in ether solvents by Weissman and Atherton[44] have indicated that the sodium ion is in rather close proximity to the naphthenide framework (contact-ion pair) in THF. With DME as solvent, however, they exist as solvent separated or loose ion pairs. Heats and entropies of dissociation carried out on the same systems by Szwarc and coworkers[45] confirmed these findings.

Thus, in the reaction of sodium naphthalene with a substrate which offers the possibility of both the electron transfer and the nucleophilic pathway, such as phenylacetonitrile, it has been shown that the product distribution can be varied by as much as 45% by varying the solvents from THF-diethyl ether (50:50) to THF-tetraglyme (50:50).[41]

Hexamethylphosphoramide[5,46-53] (HMPA), also called tris(dimethylamino)phosphine oxide, is a polar aprotic solvent which dissolves alkali metals slowly[51] to give blue paramagnetic solutions[51-56] up to 1 M in the metals[52] (eq. 4).



(4)

No other aprotic solvent demonstrates this ability. These solutions decompose after several hours with a loss of paramagnetism, accompanied by a change of colour (blue to red).[52]

However, the stability of these NaHMPA solutions can be markedly enhanced by the addition of various cosolvents[49,55]. THF is a particularly convenient one.[55,56]

The esr spectrum of HMPA$^{\dot{-}}$ [5,49,52,53,55], independent of the cation used, consists of a single sharp line at $g = 2.0022$[55], identical with the value for that of sodium in liquid ammonia. This single line esr spectrum has been interpreted in two ways; (a) as being due to a solution of phosphoryl radical anions undergoing rapid electron transfer, or (b) due to a solution of solvated electrons. According to Normant, the active species is the radical anion which slowly disproportionates to a dianion (red color) or a mixture of anions[5,49] (eq. 5 and 6).

$$2[R_3P{=}O]^{\dot{-}} \rightleftharpoons R_3P{=}O + R_3\bar{P}\text{-}\bar{O} \qquad (5)$$

$$R_3\bar{P}\text{-}\bar{O} \rightleftharpoons \bar{N}(CH_3)_2 + R_2\bar{P}\text{-}O \qquad (6)$$

$$\text{where } R = N(CH_3)_2$$

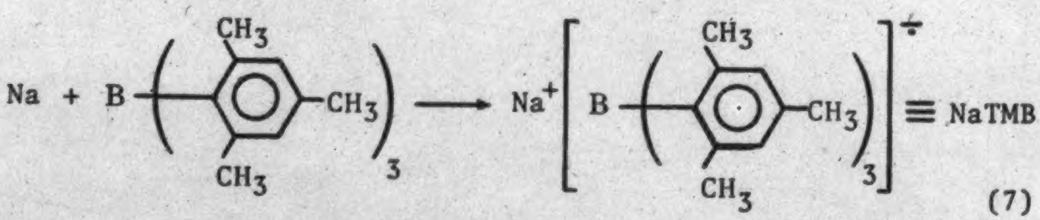
Dimethylamine is isolated after hydrolysis of the "dianion" solutions. Similarly, alkylation leads to the isolation of alkylphosphoramides and the alkyldimethylamine.

Other authors have interpreted the esr spectrum differently and believe NaHMPA to be a solution of solvated electrons similar to solutions of alkali metals in liquid ammonia.[52,55]

HMPA has an exceptional ability to strongly coordinate with cations (owing to the easy steric accessibility of the $O^{\delta-}$). Thus, the reactivity of an anion dissolved in HMPA is markedly enhanced and furthermore it exists as a "free" anion.[57] Since "free" radical anions favour electron transfer processes over those of protonation, it is reasonable to expect that electron transfer processes should be preferred in NaHMPA.

The third radical anion studied was sodium trimesitylboron (NaTMB). The reaction of triarylboron reagents with alkali metals in ethereal solvents may proceed with the transfer of either one or two electrons to form coloured salts. These reagents were first studied by Krause and coworkers.[58,59] However, TMB represents a unique example in this class.

TMB was first prepared by Dodson[60], and soon after, it was reported to react readily with sodium in THF, forming a dark blue solution of the mono sodium radical anion, $Na^{+}TMB^{\dot{-}}$[7] (eq. 7). These blue solutions are



(7)

stable for extended periods of time[7], and furthermore, the bulky mesityl group serves to impede dimerization of the radical anion as well as to inhibit formation of quaternary boron compounds[6,61] or rapid reaction with protic substances.[63]

The esr spectra of $Na^+TMB^{\cdot-}$, $K^+TMB^{\cdot-}$, and the $TMB^{\cdot-}$ solution obtained by electrolytic reduction in ethereal solvents were all identical[61,62], as was that of $Na^+TMB^{\cdot-}$ in liquid ammonia.[64] All spectra indicated that there was no metal coupling; thus, the metal ion is not in contact with the $TMB^{\cdot-}$ (i.e., the $TMB^{\cdot-}$ is a "free" ion).

The geometry of NaTMB also plays an important role in its chemistry. Griffin and van Willigen interpreted their esr data for $Na^+TMB^{\cdot-}$ as reflecting the fact that steric hindrance between the ortho-methyl groups causes a significant nonplanarity of the mesityl rings, which results in effective shielding of the position of highest charge density (the boron atom) in $Na^+TMB^{\cdot-}$.[61] This inhibits "tight" ion pair formation.

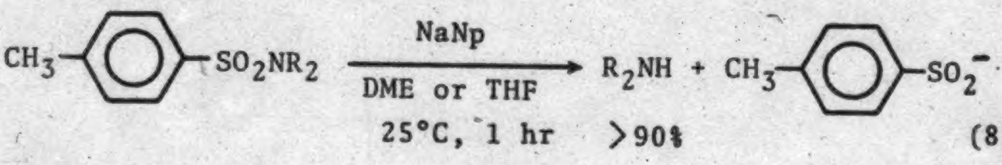
As a result, $Na^+TMB^{\cdot-}$, like $Na^+HMPA^{\cdot-}$, would be anticipated to display a preference for electron transfer rather than "protonation" processes. In fact, because of the remarkable stability towards decomposition of the $Na^+TMB^{\cdot-}$ and its slow reaction with protic substances, the radical anion of TMB could be expected to undergo electron transfer processes only.

Not only may relatively stable radical anions be formed by chemical reduction, but also by electrolytic and photolytic methods.[65-68] The parent molecule must possess a sufficiently low-lying empty orbital for acceptance of the odd electron. In addition to numerous aromatic hydrocarbons[1,2,11,69-71] and compounds containing phosphorus[5,55,56,65,67], boron[6,61,62], silicon[65,67,68], nitrogen[5,65,67] or transition metals[67,71], there are various additional classes of compounds which exhibit this capability of accepting an electron and forming a radical anion. These include unsaturated compounds containing conjugated bonds and electron withdrawing groups such as tetracyanoethylene[67], tetraphenylethylene[11,72], aryl ketones[71], enones[73], diones[65,71,74], triones[65,74-77], azo compounds[65], nitro compounds[65-67], and heterocycles [67,71,78,79].

Radical anion solutions are very reactive towards a wide variety of substances, such as water[17-19,80]. oxygen[7], hydrogen[81-83], nitrogen[84], carbon monoxide[85], carbon dioxide[5,16,86], sulphur dioxide[87], isoprene[88,89], alkyl[19-38] and aryl[39,40,90] halides, ethers[5,91], and many other "electrophilic" organic compounds.[3,5,55,56,63,92-102].

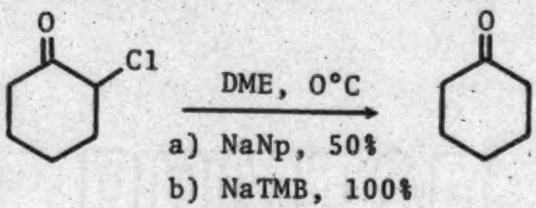
The versatility of these reagents as electron transfer reagents and as tools for organic synthesis is evident by the many transformations which they can accomplish. Some representative reactions are shown below:

(1) Cleavage of sulphonamides to amines.[94,95]


CH3
SO2NR2
NaNp
DME or THF
25°C, 1 hr
R2NH + CH3
SO2-
>90%

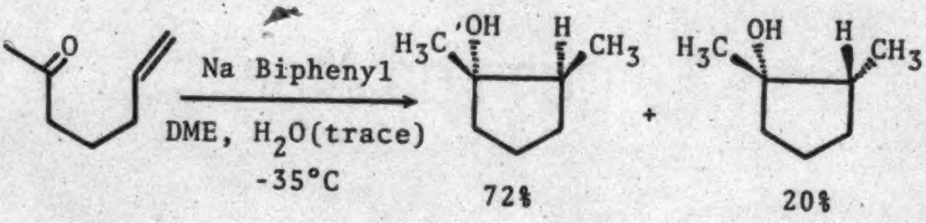
(8)

(2) Reductive dehalogenation of α-haloketones.[3]

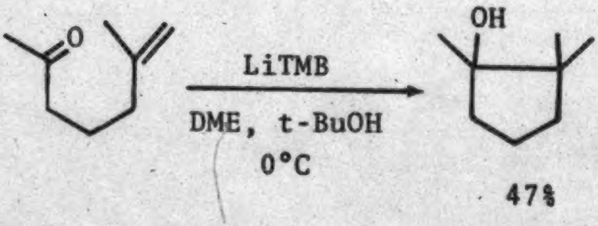

O
Cl
DME, 0°C
a) NaNp, 50%
b) NaTMB, 100%
O

(9)

(3) Reductive cyclization of unsaturated ketones (enones, ynones and allenic ketones).[3]

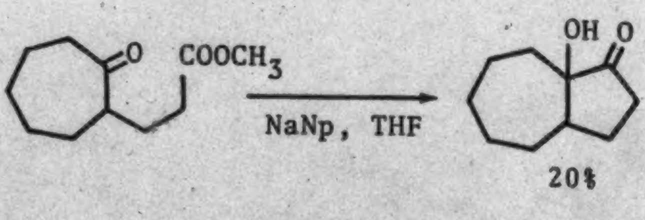

O
Na Biphenyl
DME, H2O(trace)
-35°C
H3C
OH
H
CH3
72%
+
H3C
OH
H
CH3
20%

(10)


O
LiTMB
DME, t-BuOH
0°C
OH
47%

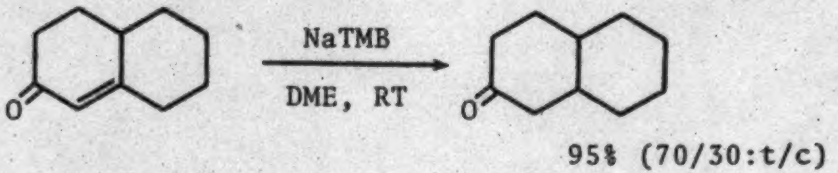
(11)

(4) Cyclization to fused ring systems via acyloin-type condensations.[100,101]

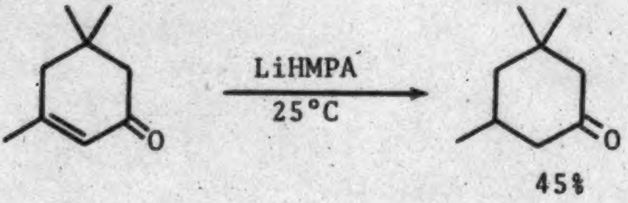

O
COOCH3
NaNp, THF
OH
O
20%

(12)

(5) Reduction of α,β-unsaturated ketones.[63,102]

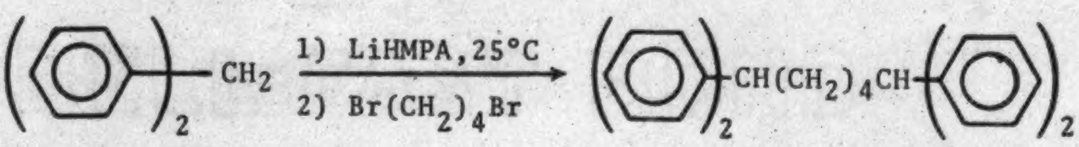

NaTMB
DME, RT
O
O
95% (70/30:t/c)

(13)


LiHMPA
25°C
O
O
45%

(14)

(6) Alkylation reactions.[5]

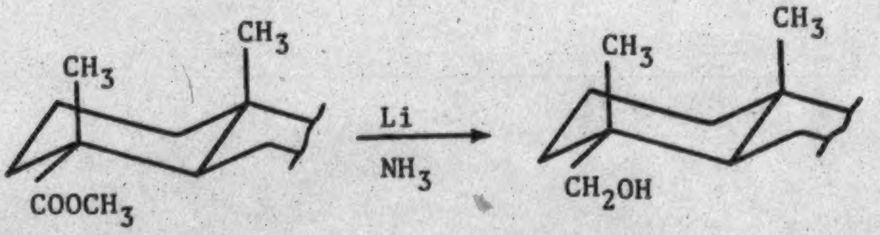

CH2
2
1) LiHMPA,25°C
2) Br(CH2)4Br
CH(CH2)4CH
2
2

(15)

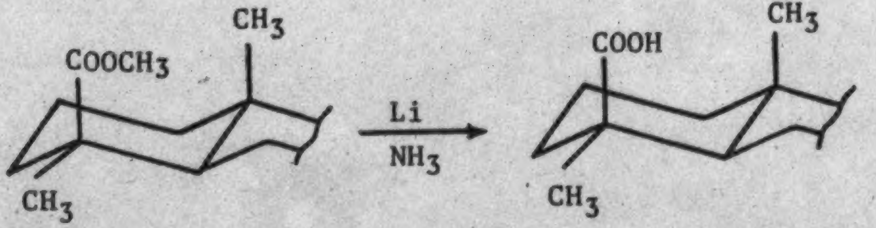
THE REACTION OF SODIUM NAPHTHALENE, SODIUM HEXAMETHYLPHOSPHORAMIDE AND SODIUM TRIMESITYLBORON WITH STERICALLY HINDERED ESTERS

INTRODUCTION

In 1958, Wenkert and Jackson[103] reported a method for the reductive hydrolysis of hindered esters by treatment with lithium in liquid ammonia. This method was also recommended as a diagnostic tool for differentiating between axial and equatorial esters in rigidly held ring systems. The less sterically hindered equatorial esters were reduced to alcohols (eq. 16), whereas the axial epimers underwent reductive hydrolysis to the corresponding acids (eq. 17).



(16)



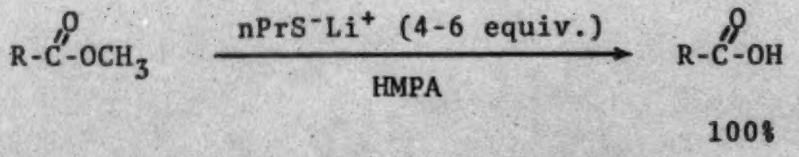
(17)

Then, in 1963, Gutsche and Tao[100] showed that the keto ester, methyl β-(2-ketocycloheptane) propionate, could be cyclized to 7-hydroxy-8-ketobicyclo [5.3.0] decane by treatment with a THF solution of sodium naphthalene (eq. 12). These observations led to the expectation that electron transfer from a radical anion to a hindered ester would be a facile process.

Furthermore, at the commencement of this work only a few methods were available to effect reduction of sterically hindered esters. These involved reagents such as lithium iodide in refluxing pyridine, 2,6-lutidine, or 2,4,6-collidine[104]; potassium tert-butoxide in dimethylsulfoxide (DMSO)[105]; and lithium iodide or bromide in hot dimethylformamide (DMF)[106]. Some of these reaction conditions are rather drastic.

During and since the completion of the work done in this thesis, totally new methods for such reductions [107-109], all giving yields greater than 90% of acid, have been described.

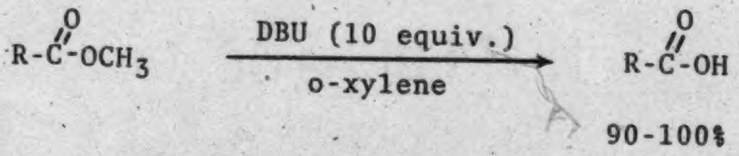
Bartlett and Johnson employed lithium n-propyl mercaptide in HMPA to cleave methyl esters under mild conditions (eq. 18)[107]. The reaction proceeded readily



$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OCH_3 \xrightarrow[\text{HMPA}]{nPrS^-Li^+\ (4\text{-}6\ \text{equiv.})} \underset{100\%}{R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH} \qquad (18)$$

at room temperature, and the products were isolated in quantitative yields. Moreover, the reagent is compatible with the presence of acid-or base-sensitive functionalities.

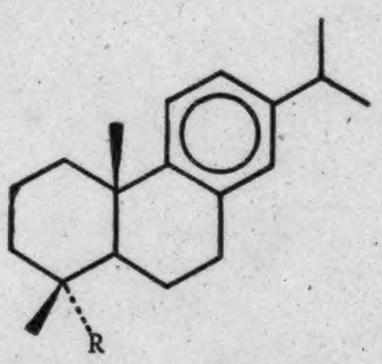
The use of boron trichloride (4 equiv.) in methylene chloride at 0°C has also been described[108] for that purpose. The third, and most general method, which can also be applied to non-hindered esters, uses 1,5-diazabicyclo [5.4.0] undecene-5 (DBU) in o-xylene at reflux temperatures (eq. 19)[109]. Yields of acid for the latter two methods are similar and > 90%.



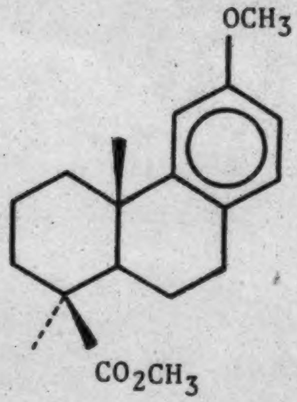
$$\mathrm{R{-}\overset{O}{\overset{/\!/}{C}}{-}OCH_3} \xrightarrow[\text{o-xylene}]{\text{DBU (10 equiv.)}} \underset{\text{90-100\%}}{\mathrm{R{-}\overset{O}{\overset{/\!/}{C}}{-}OH}} \qquad (19)$$

The sterically hindered esters chosen for the present study were methyldehydroabietate (1a), an equatorial ester, methyl O-methylpodocarpate(2), an axial ester, and methyl mesitoate (3a), a hindered aromatic ester. These same model systems were employed in the Wenkert study and it was thus possible to make a comparison between the results of the two methods.

It was also hoped that by investigating this reaction with a variety of radical anions, some understanding of the nature and use of these reagents in synthetic organic chemistry could be gained.



1 a, R= $COOCH_3$
b, R= CH_2OH
c, R= $COOH$
d, R= $CONHCH_3$
e, R= $CON(CH_3)_2$



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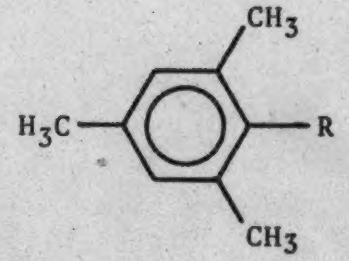
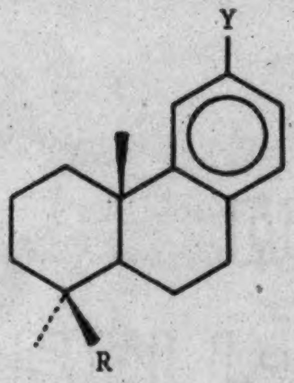


3 a, R= CO_2CH_3
b, R= CH_2OH
c, R= $COOH$

RESULTS AND DISCUSSION

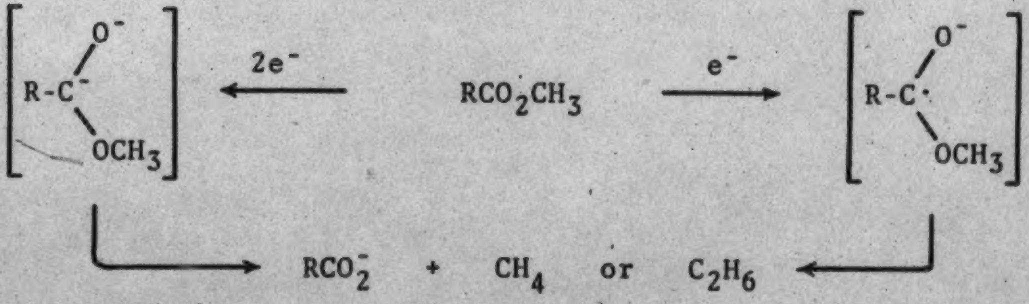
Wenkert reported that treatment of methyl podocarpate (4b) with lithium in liquid ammonia led to a 62% yield of podocarpic acid (4a). This hydrolysis, a "reductive" process, was formalized by Wenkert in the following way (Scheme II):



4

a, R= COOH, Y= OH
b, R= $COOCH_3$, Y= OH
c, R= COOH, Y= H
d, R= $COOCH_3$, Y= H
e, R= CH_2OH, Y= H
f, R= COOH, Y= OCH_3
g, R= $COOCH_3$, Y= OCH_3
h, R= CHOH-naphthyl, Y= OCH_3
i, R= CH_2-naphthyl, Y= OCH_3
j, R= $CONHCH_3$, Y= OCH_3

Scheme II


O⁻
R-C⁻
OCH₃
2e⁻
RCO₂CH₃
e⁻
O⁻
R-C·
OCH₃
RCO₂⁻
+
CH₄
or
C₂H₆

This ability to form the acid rather than the alcohol has been interpreted as being due to resistance of the axially trigonal carbonyl carbon atom to expand to the more sterically demanding tetrahedral state. While the fate of the methyl function had not been ascertained, it was suggested that most probably the group was reduced to methane or ethane.

While this reaction appeared to be useful as an easy means of hydrolyzing highly sterically hindered esters, it also suggested itself as a diagnostic tool for differentiating between axial and equatorial carbonyl groups in rigidly held ring systems. Esters of less sterically hindered acids are expected to be reduced to the corresponding alcohol, whereas hindered esters should undergo reductive hydrolysis to the acid (see eq. 16 and 17).

Three esters studied by Wenkert gave results which supported this hypothesis.

Methyl desoxypodocarpate (4d), an axial ester, on treatment with metal-ammonia solutions, gave a 77% yield of the acid (4c) and a 23% yield of the alcohol (4e). However, methyl dehydroabietate (1a), an equatorial ester, afforded 3% dehydroabietic acid (1c) and 62% dehydroabietinol(1b). The sterically hindered aromatic ester, methyl mesitoate (3a), was reduced exclusively to the alcohol, 3b.

Reactions with Sodium Naphthalene

Our initial attempts to study the feasibility of employing a radical anion solution for ester reductions were carried out with sodium naphthalene (NaNp) in THF at room temperature on methyl-O-methyl podocarpate (4g) as substrate.

Preliminary experiments showed that at least two molar equivalents of NaNp were necessary for complete utilization of the ester. Also, inverse addition (i.e., addition of the radical anion solution to a solution of the ester) gave the same yield of acid as did normal addition.

When one equivalent of axial ester, 4g, in THF was added (10 minutes) to 2.3 equivalents of NaNp in THF, two solids were obtained as the major products. Acid 4f was produced in 34% yield and the other product (24% yield) was alcohol 4h, derived from alkylation of the ester by the naphthalene moiety. Furthermore, when the reaction was repeated with a large excess of NaNp (6.6 equiv.), the amount of alkylation products increased. Correspondingly, the yields of products 4f and 4h decreased (17% and 16%, respectively), and a third compound, 4i, was isolated as the major product in 54% yield (see Table I, entries 1-4).

TABLE I

Reduction of Hindered Esters with Sodium Naphthalene in Tetrahydrofuran

Substrate		Molar Ratio[a]	Time[b] (min)	Temp (°C)	Products (% yield)[c]				
					R-COOH	$R\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}R$	$R\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}\overset{OH}{\overset{\vert}{CH}}\text{-}R$	$R\text{-}\overset{OH}{\overset{\vert}{CH}}\text{-}R'$	$R\text{-}CH_2\text{-}R'$
1.	**4g**	1:2.1	70	25	28	0	0	25	0
2.	**4g**	1:2.3	70	25	34	0	0	24	0
3.	**4g**	1:6.6	70	25	17	0	0	16	54
4.	**4g**	1:2.3[d]	70	25	34	0	0	--	--
5.	**4g**	1:20.7[e]	45	0	0	0	0	0	0
6.	**1a**	1:2.8	70	25	4	--[f]	--[f]	0	0
7.	**3a**	1:2.0	60	25	5	34	16	0	0

(a) Substrate (ester): sodium naphthalene.

(b) Time of addition (10 min) plus additional stirring period.

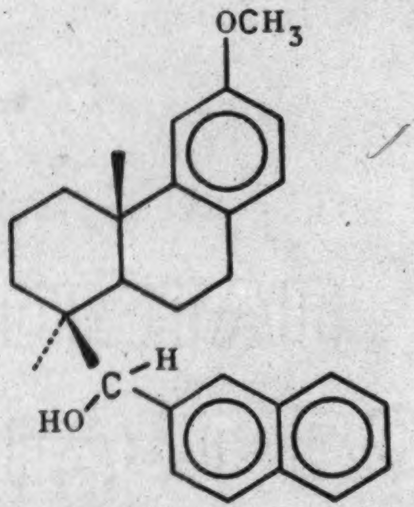
(c) Isolated yields.

(d) Inverse addition.

(e) Contained 3.8 equiv. of *t*-butyl alcohol.

(f) Neutral products were obtained but not identified.

Compound 4h was assigned structure 5, that of O-methylpodocarpyl 2-naphthyl carbinol on the basis of spectroscopic (nmr and mass spectra) and chemical studies (oxidation to the corresponding ketone).



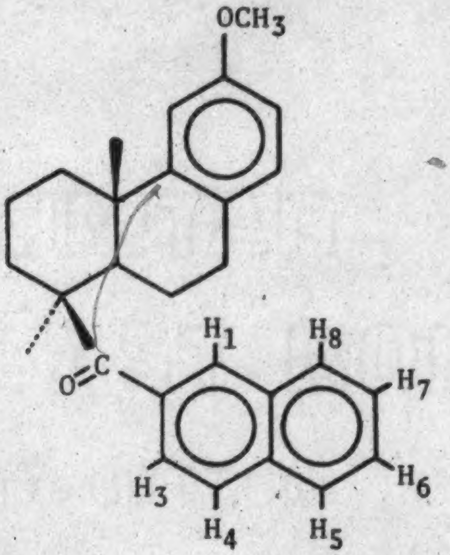
5

The nmr spectrum (pyridine-d_5, 100 MHz) of 5 exhibited the following absorptions: a sharp singlet for 3 protons at δ1.07 (-C$\underline{H}_3$ on C_4), a sharp singlet for 3 protons at δ1.56 (-C$\underline{H}_3$ on C_{10}), a multiplet from δ1.20 to 2.95 for 11 aliphatic protons, a sharp singlet for 3 protons at δ3.66 (Ar-OC$\underline{H}_3$), a doublet for 1 proton (J=2Hz) at δ5.72 (-C$\underline{H}$OH-) which collapsed to a singlet on D_2O exchange, and a broad singlet for one proton located at δ6.42 (-OH), which exchanged with D_2O. Since the hydroxyl proton is coupled to the one absorbing at δ5.72, the hydroxyl group must be in a relatively fixed position. Absorption for the phenyl ring of the podocarpyl skeleton appeared at δ6.80 (3H,m). The seven naphthyl protons absorbed at δ7.46 (3H,m), 7.85 (3H,m) and 8.19 (1H,s).

The proton at C-1 in various 2-substituted naphthalenes appears as a sharp singlet and is readily identified. In addition, the shifts induced on the C-1 hydrogen due to a substituent at the 2-position further aids in their identification.[110] Therefore, the nmr spectrum of 5 indicates that the linkage of the naphthalene moiety is at the 2-position.

Mass measurements of 5 gave a molecular ion of 400.2394 (calcd for $C_{28}H_{32}O_2$:400.2402). The mass spectra of the starting ester, 4g, and the product alcohol, 5, showed major differences in their respective fragmentation patterns and each possessed different base peaks (227 and 161, respectively). Compound 4g displayed the typical fragmentation of a podocarp-8,11,13-triene derivative possessing oxygenation in the saturated part of the molecule.[111-113] In contrast, initial fragmentation of 5 led to a podocarp-8,11,13-triene derivative lacking oxygenation in the saturated part of the molecule.[113,114]

Collins oxidation[115] of 5 led to the corresponding ketone, 6, ir: 1670 cm^{-1} (conjugated $>C=O$), the structure of which was confirmed by additional spectroscopic data (nmr and mass spectrum). The mass measurement

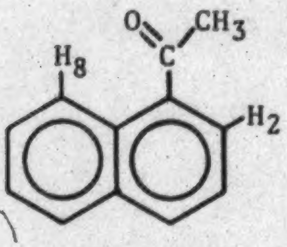


6

was 398.2258 (calcd for $C_{28}H_{30}O_2$:398.2246) and the fragmentation pattern of 6 was similar to that of 5, and gave the same base peak (m/e 161).

The nmr spectrum ($CDCl_3$, 100 MHz) of 6 showed absorptions similar to those of the O-methylpodocarpyl skeleton absorptions in 5 (see Experimental). The nmr spectrum showed absorptions for the seven naphthyl protons at δ7.57 (3H,m), δ7.83 (2H,m), δ7.89 (1H,d,J=8 Hz) and δ8.05 (1H,s).

These results are in accord with observations by Martin and coworkers, who measured the nmr spectra of 1- and 2- acetylnaphthalenes[116] (7 and 8).



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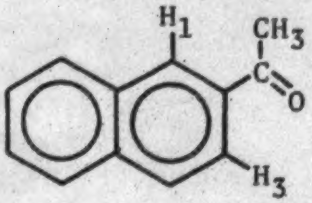

8

1-Acetylnaphthalene, 7, showed two well separated resonances for the naphthyl protons in the ratio of 1:6. The hydrogen at C-8 (H_8) appeared as a multiplet at δ8.76. For 2-acetylnaphthalene, the hydrogens at C-1 (H_1) and C-3 (H_3) appeared as a singlet at δ8.42 and a doublet at δ8.04, respectively, downfield from the remaining five protons which were further separated into two multiplets at δ7.88 and δ7.55 in the intensity ratio of 3:2. This latter spectrum is in agreement with our observations for ketone 6.

Measurement of the nmr spectrum in the presence of the shift reagent [Eu(fod)$_3$] provided additional support for the β-linkage assigned to 6. The observed chemical shifts of the protons H_1 and H_3 of the naphthalene ring for 6 are given in Table II. Since the isotropic shifts decrease with increasing distance of the respective nuclei from the bonding site[117,118] of the [Eu....O=C] complex, the assignment of the position of attachment of the carbonyl to the naphthyl moiety can be made by comparing the changes in chemical shifts (Δδ). In the presence of [Eu(fod)$_3$], protons H_1 and H_3 were shifted downfield by the same magnitude and appeared as a singlet (H_1) at δ10.09 as a doublet (H_3) at δ9.93 (J=8Hz), respectively. Had the bonding been to the α-position (see structure 7), the absorptions due to H_2 and H_8 would be expected to undergo chemical shifts of different magnitudes and, furthermore, both would have appeared as multiplets downfield. This provides support for the β-linkage assigned.

Compound 4i, the major product of the reaction of 4g with 6.6 equiv. of NaNp, was assigned structure 9. Mass

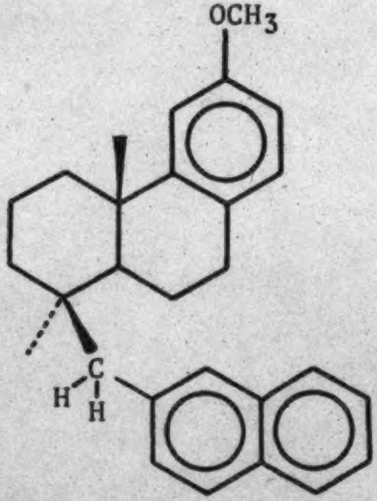

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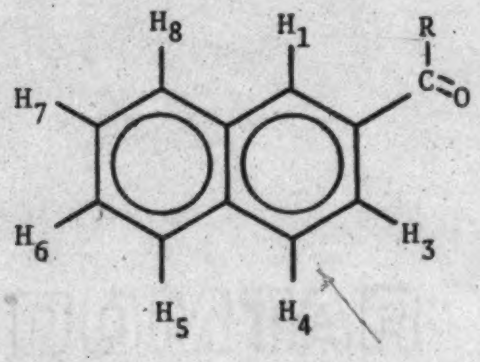
TABLE II

Chemical Shifts[a] for O-Methylpodocarpyl 2-Naphthyl Ketone



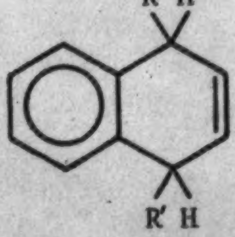
	H_1	H_3
Normal	8.05	7.89
$Eu(fod)_3$[b]	10.09	9.93
Δ δ	2.04	2.04

(a) Given in δ units, measured at 100 MHz in $CDCl_3$.

(b) Ca 0.5 equivalents of shift reagent.

measurement revealed a molecular weight of 384.2444 (calcd for $C_{28}H_{32}O$: 384.2453). The nmr spectrum ($CDCl_3$, 100 MHz) showed, for the 7 naphthyl protons, absorption as a doublet of doublets for one proton (H_3) at δ8.18, as a multiplet for two protons at δ7.77 and as a multiplet for four protons at δ7.41; in pyridine-d_5 as solvent, the naphthyl protons appeared as a doublet (J=8Hz) for one proton (H_3) at δ8.34, as a multiplet for two protons at δ7.88 and as multiplet for four protons at δ7.50. The observed doublet is indicative of the β-linkage (a downfield multiplet would have been observed if the linkage had been to the α-position).

Alkylation products arising from reactions of organic halides with sodium naphthalene have been reported previously[23,24,33,39,40], but the majority of these are of a different type than those observed here. Usually, 1,4-dihydronaphthalene derivatives (10) result, wherein the naphthalene ring has been monoalkylated at the α-position, or dialkylated at positions 1 and 4.[33] An



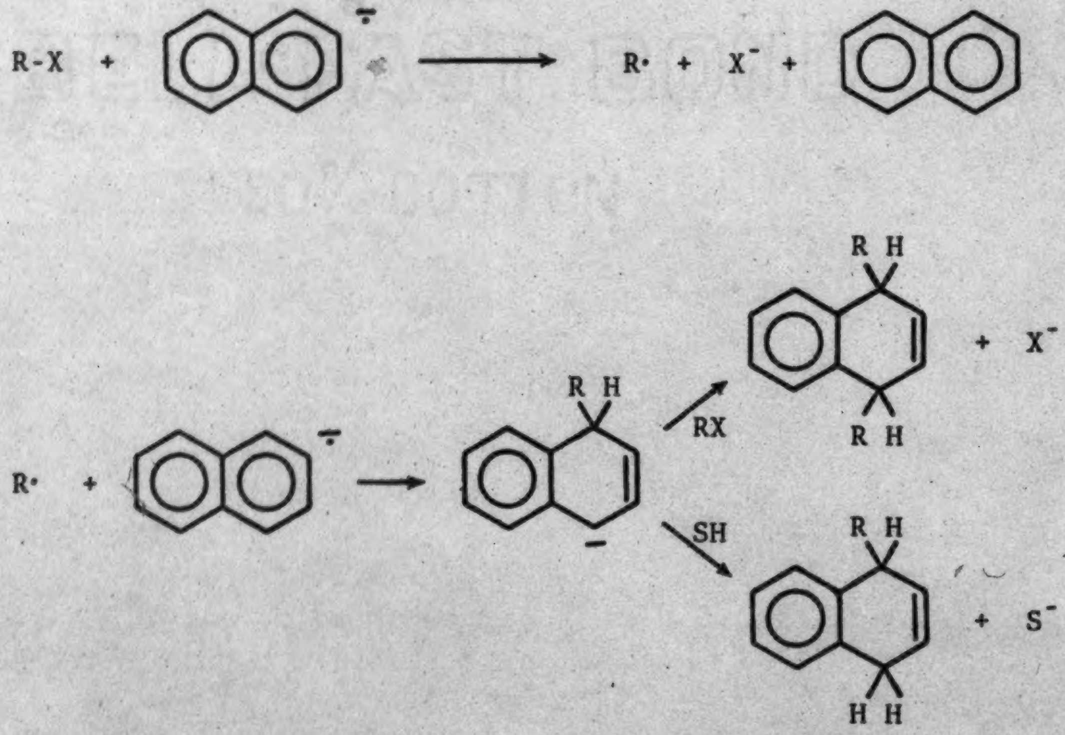
where R′ = R
R′ = H

10

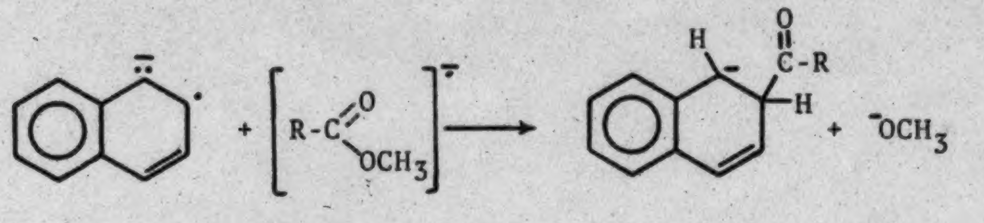
exception is the reaction of aryl halides[39,40] which give at most 2 to 4% of α- and β-arylated naphthalenes in an approximately 1:1 ratio, resulting from aryl radical-radical anion coupling.[39]

Sargent and Lux[33], as well as Garst and coworkers[32], have postulated the following mechanism for the formation of structures such as 10 (Scheme III), and have also noted that the yields and ratios of products were wholly insensitive to the presence of excess naphthalene.[33]

Scheme III



The observation in the present study of β-alkylation is (at least formally) the result of a coupling process between the β-position of the naphthalenide species with the aryl carbon of the ester function (eq. 20).



(20)

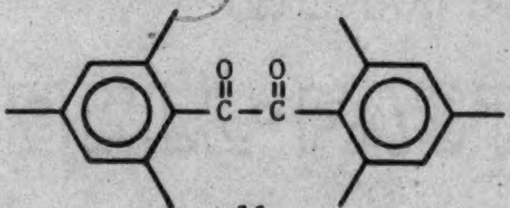
The product of such a reaction would be, initially, a ketone 9 which upon further reduction would give rise to 5, the benzylic alcohol. Similar observations have been made in related systems. For example, Hall and coworkers have reported the reduction of alkyl aryl ketones, Ar-CO-R, to benzylic alcohols, and thence to hydrocarbons using lithium in liquid ammonia.[119] There is thus precedence for the reduction products observed in the present study.

Further difficulties were encountered when the reaction was extended to the remaining two hindered esters.

With the equatorial ester, methyl dehydroabietate (1a), and 2.8 equiv. of sodium naphthalene (see Table I, entry 6), only a 4% yield of the acid, 1c, was realized. The neutral fraction (remaining 95% of the products) proved to be (by tlc) a mixture of at least six compounds.

Owing to the complexity of the mixture, these products could not be successfully separated or identified. However, the mixture was shown not to contain the starting ester, the alcohol (1b), nor any naphthalene alkylated products.

The sterically hindered aromatic ester methyl mesitoate (3a) reacted with 2.0 equiv. of sodium naphthalene (see Table I, entry 7) to give, in addition to the acid 3c (5%), two coupling-type products. Mesitil (11) and mesitoin (12) were isolated in 34 and 16% yields,



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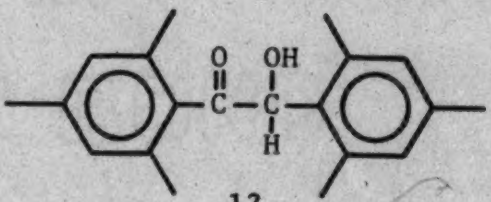


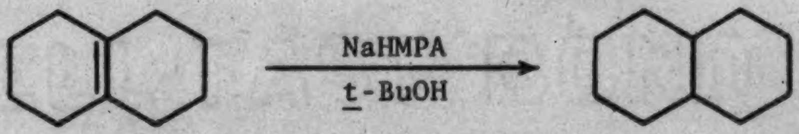
12

respectively. At least two other neutral compounds were also formed which could not be identified.

The presence of mesitoin suggested that it may arise from over-reduction of mesitil. To test this possibility, benzil was employed in the reaction rather than mesitil due to the limited amount of mesitil available. Treatment of benzil with two equivalents of NaNp gave benzoin in >75% yield. This experiment thus offered the possibility that mesitoin could result from over-reduction of mesitil.

Reactions with Sodium Hexamethylphosphoramide

Several studies have been reported involving the use of sodium HMPA as a reducing agent. Whitesides and Ehmann reported the reduction of olefins using sodium-HMPA-_t_-butyl alcohol.[120] This reducing mixture provided a convenient and general method for reducing carbon-carbon double bonds. Even tetraalkyl substituted olefins were saturated with ease (eq. 21).



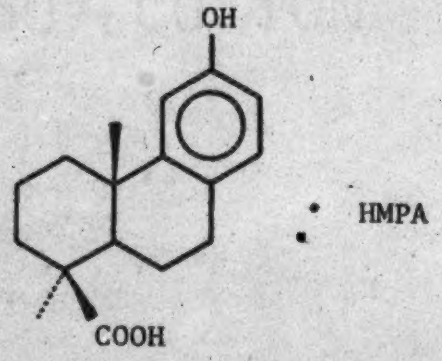
(21)

91% trans,3% cis

House and coworkers have studied the reduction of enones with sodium-HMPA both in the presence and absence of a proton source (H_2O, D_2O, MeOH, and t-BuOH).[55,56] Reaction conditions were varied substantially (i.e., the amount of sodium used, the amount of proton donor, the reaction temperature, the time, and the order of mixing), in an effort to determine how these parameters would affect the yields and ratio of products formed. Also, it was noted that the use of THF as a cosolvent markedly enhanced the stability of the sodium-HMPA solution. As a result, most reactions were run in a 2:1 HMPA-THF solvent system. These blue Na-HMPA-THF solutions were stable for periods of one hour or more at 0°C after the addition of tertiary alcohols such as _t_-BuOH.

It was thus of interest to explore the sodium HMPA system for the reduction of the hindered esters to make a comparison with those results obtained previously with sodium naphthalene.

When a solution of methyl-O-methyl-podocarpate (4g) was added slowly to Na-HMPA-THF (Table III, entry 1), the reaction was exothermic and a gas was evolved. A mixture of podocarpic acid (4a) and the podocarpic acid-HMPA 1:1 complex (13) was isolated in _ca_ 70% yield.* The complex,



13

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* This yield was likely higher owing to loss of the water soluble complex to the aqueous extracts. Less than 7% of neutral products were obtained.

TABLE III

Reactions[a] of Hindered Esters with Sodium Hexamethylphosphoramide - Tetrahydrofuran[b] Solutions

Entry	Substrate	NaHMPA-THF[c] (equiv.)	Proton Source (equiv.)	Temp (°C)	Time (min) for		Products (% yield)[d]
					Addition	Mixing	
1.	4g	>2	--	25	55	5	4a + 13 (>70)[e]
2.	4g	4.1	--	0	0.5	5	4f (89), 4j (8)
3.	4g	7.4	t-BuOH (2.7)	0	0.5	5	4f (73), 4j (24)
4.	1a	>2	--	25	80	5	1c (4)[e], 1d(66)
5.	1a	3.5	--	25	25	5	1c (44), 1d(36)
6.	1a	2.7	--	0	0.5	5	1c (56)[e], 1d (2 - 4)
7.	1a	2.5[f]	--	0	0.25	5	1c (70), 1d (trace)
8.	1c	2.1[f]	--	0	0.25	30	1c (100)
9.	1e	<2	--	0	3	30	1d (50), 1e (50)
10.	3a	2.3	--	0	0.5	5	7 products
11.	3a	4.7	t-BuOH (1.5)	0	0.5	5	7 products

(a) All reactions were carried out under an atmosphere of nitrogen or argon.

(b) Solvents were 2 : 1 in HMPA-THF.

(c) Number of equivalents relative to substrate as 1.0.

(d) Isolated yields.

(e) Yields of acids would be higher, due to loss by complexing with HMPA.

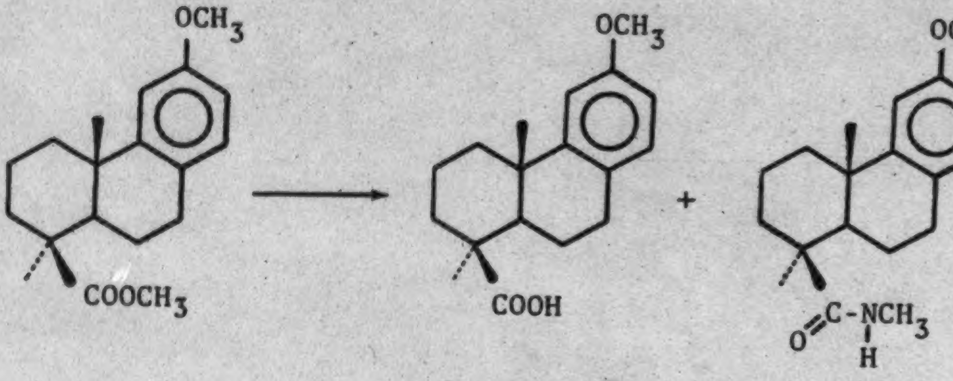
(f) Inverse addition.

13, was isolated as colourless crystals, mp 154-156°C; mass spectrum, m/e, M^+ 274. The mass spectrum exhibited fragmentation peaks which were essentially superimposable on those of the mass spectra of HMPA and podocarpic acid taken independently.

Thus, both the ester and the ether linkages had been cleaved under these conditions with NaHMPA.

The cleavage of ethers, Ar-O-R, by solutions of alkali metals in HMPA has been previously observed by Normant.[121] Although dialkyl ethers are not cleaved, mixed alkyl aryl and diaryl ethers give phenols and phenol-HMPA complexes. For example, phenetole gives phenol (20%) and 65% of phenol-HMPA upon reaction with potassium in HMPA.[121] Thus, our observation of ether cleavage and formation of an HMPA complex with podocarpic acid finds precedence in the French workers' studies.

However, cleavage of the methyl ether could be prevented. When the reaction temperature was reduced to 0°C and a fast addition rate was employed (Table III, entries 2 and 3), O-methylpodocarpic acid (4f) was the major product along with a small amount of N-methyl-O-methylpodocarpamide (4j) (eq. 22). No difficulties were encountered with HMPA forming complexes with the products of this reaction, and only the ester group was involved in the reduction.



(22)

4f (89%)   4j (8%)

When the reaction was repeated in the presence of _t_-butyl alcohol as a proton source, the ratio of 4f:4j decreased to _ca_ 3:1.

The structure proof of N-methyl-O-methylpodocarpamide (4j) was based on the following spectral data. The infrared spectrum showed a sharp band at 3490 cm^{-1} (amide-NH), and an amide carbonyl absorption at 1650 cm^{-1}. The molecular weight was determined as 301.2038 (calcd for $C_{19}H_{27}NO_2$:301.2043) by high-resolution mass spectroscopy. The nmr spectrum exhibited the characteristic resonances observed for the O-methylpodocarpyl system, and in addition, showed a doublet (J=5Hz) at δ2.85 (3H,N-C$\underline{H}_3$) and a broad singlet at δ5.74 (1H,N$\underline{H}$) which exchanged slowly with D_2O.

The reactions of the equatorial ester, methyl dehydroabietate (1a), gave similar results (Table III, entries 4 to 7). As the temperature and time for addition were decreased, the amount of acid formed increased with a resultant decrease in amide production. Entry 7 illustrates the important effect of addition time. When the Na-HMPA-THF solution was added quickly (15 sec.) to a solution of 1a at 0°C, a 70% yield of acid 1c, was obtained. Difficulties were encountered in isolating this equatorial acid (1c). Apparently HMPA forms a stronger complex with the equatorial acid than with the axial acid. Dehydroabietic acid (1c) was isolated by "salting" out the aqueous extracts.

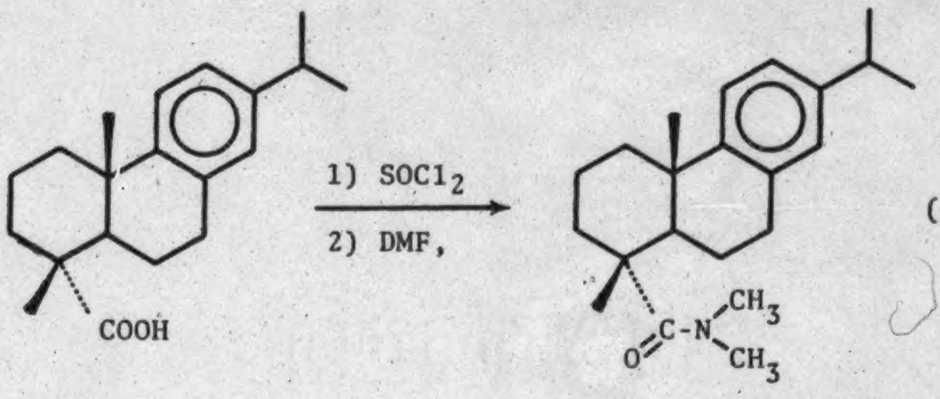
In one run (Table III, entry 6) it was found that the acid could be liberated from the dehydroabietic acid: HMPA complex by acid exchange (i.e., by refluxing with a small amount of acetic acid in THF). This treatment simply replaced acetic acid for dehydroabietic acid, since, as a stronger acid, HOAc presumably forms a more stable complex with HMPA.

The amide formed in the above reactions was identified as N-methyldehydroabietamide (1d) on the basis of spectral data. The infrared spectrum ($CHCl_3$) exhibited absorptions for an amide NH (3490 cm^{-1}) and an amide carbonyl (1650 cm^{-1}). The mass spectrum showed a molecular ion of 313 (calcd 313). The nmr spectrum ($CDCl_3$) showed absorption for one hydrogen as a broad singlet at ca $\delta 5.87$ (NH) and absorption for three hydrogens as a doublet at $\delta 2.75$ with J=5Hz($N-C\underline{H}_3$). The remaining nmr absorptions were consistent with the dehydroabietyl skeleton (see Experimental).

The formation of the monomethyl amide in these experiments was somewhat surprising. Solutions of NaHMPA reportedly undergo slow disproportionation to a mixture of anions[5,49] (eq. 6), one of which is the dimethylamine anion. It seemed reasonable to expect the dimethyl (1e) rather than the monomethyl amide (1d) as product. To account for the formation of the monomethyl amide, two possible reaction sequences were investigated.

To test whether it could derive directly from the acid (anion), 1c was treated with 2.1 equiv. of NaHMPA-THF (Table III, entry 8). No amide was produced, and the acid was recovered (100%) as its sodium salt. We then tested whether the N,N-dimethyl amide was an intermediate which could be converted to the monomethyl amide in the presence of NaHMPA radical anion.

N,N-dimethyldehydroabietamide was prepared by converting dehydroabietic acid to the corresponding acid chloride using thionyl chloride (neat), followed by addition of dimethylformamide (DMF) and refluxing the resulting solution (eq. 23), according to the method of Coppinger.[122]

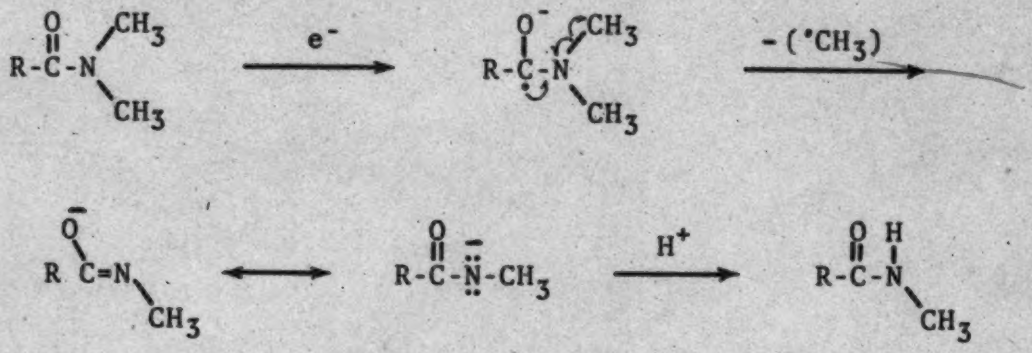


(23)

$\underline{\underline{1e}}$

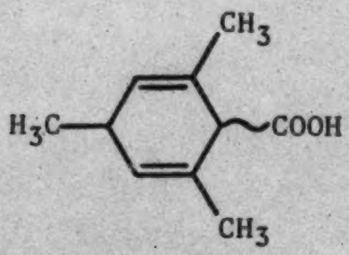
This is a simple and effective method of preparing dimethylamides and avoids the use of the somewhat objectionable dimethylamine.

When $\underline{\underline{1e}}$ was reacted with Na-HMPA-THF (0°C), the blue colour of the radical anion solution faded immediately. Upon workup only two products were isolated, N-methyldehydroabietamide, and N,N-dimethyldehydroabietamide (the starting material) in ca 50:50 ratio. Thus, the monomethyl amide ($\underline{\underline{1d}}$) could possibly arise by further reaction of the tertiary amide ($\underline{\underline{1e}}$) with NaHMPA. A plausible mechanism (analogous to the Wenkert scheme) for such a process involves initial electron transfer to the tertiary amide, loss of a methyl group (either as an anion or radical), followed by hydrolysis (eq. 24).



(24)

When the most favourable reaction conditions for reduction of the resin esters were applied to methyl mesitoate (3a), both in the presence and absence of a proton source, a complex mixture was obtained (see entries 10 and 11). Examination by tlc showed the presence of at least seven products in each reaction, but in varying amounts. Four of these were acid derivatives. The nmr spectrum (see Experimental) of the acidic mixture appeared to indicate that reduction of the aromatic ring had occurred and that the majority of the acidic fraction consisted of a mixture of epimeric acids possessing the dihydroaromatic skeleton 14.



14

Thus, with the NaHMPA-THF reducing medium, difficulties were encountered which mainly involved the physical properties of HMPA itself. This aprotic polar solvent has the ability to form very stable 1:1 complexes with carboxylic acids and phenols.[5] Freeing the desired product from complexing HMPA can be at times difficult. Furthermore, during workup procedures, care must be exercised to extract the aqueous layers extensively in order to avoid product loss in the form of water-soluble acid : HMPA (1:1) complexes (Table III, entries 1, 4 and 6). Lastly, like naphthalene, HMPA can partake in the reaction and act as an alkylating agent. However, it was observed that the amount of alkylation product (i.e., amide formation) could be controlled by varying the addition and reaction times (Table III, entries 4 to 7).

In connection with our studies on reduction of the resin esters, nmr spectral data was collected for a number of new compounds which may constitute an important addition to the body of nmr data already available for such compounds[123,124] and thus be of aid in the solution of structure problems in the chemistry of diterpenic substances.

Tables IV and V summarize the chemical shifts of the C-4 and C-10 methyl groups observed for the various podocarpyl and dehydroabietyl derivatives used or isolated in this study. Large differences in the chemical shifts of

TABLE IV

N.M.R. (100 MHz) STUDY OF THE CHEMICAL SHIFTS OF C_4 AND C_{10} METHYL GROUPS IN THE PODOCARPYL SKELETON BY VARYING R AT β-C_4

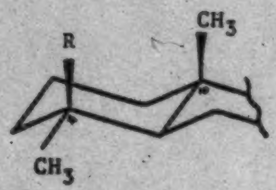
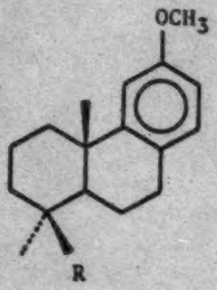
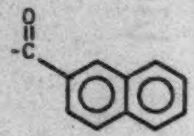
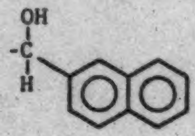
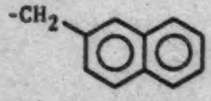
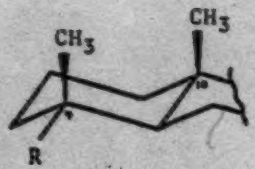
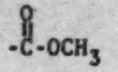
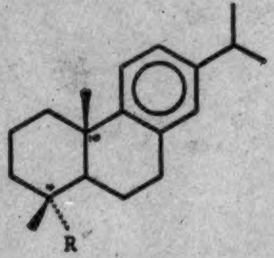
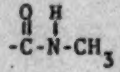
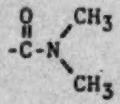
	R	Solvent	$C_{10}(\delta)$	$C_4(\delta)$	$\Delta\delta_{C_4-C_{10}}$
 	$-COOCH_3$	$CDCl_3$	1.03	1.24	0.21
		pyr-d_5	0.94	1.08	0.14
	$-CONHCH_3$	$CDCl_3$	1.18	1.32	0.14
	$-COOH$	$CDCl_3$	1.20	1.40	0.20
		$CDCl_3$	1.24	1.63	0.39
		pyr-d_5	1.19	1.44	0.25
		pyr-d_5	1.07	1.56	0.49
		$CDCl_3$	0.65	1.41	0.76
		pyr-d_5	0.62	1.38	0.76

TABLE V

N.M.R. (60 MHz) STUDY OF THE CHEMICAL SHIFTS OF C_4 AND C_{10} METHYL GROUPS IN THE DEHYDROABIETYL SKELETON BY VARYING R AT α-C_4

	R	$C_{10}(\delta)$	$C_4(\delta)$	$\Delta\delta_{C_4-C_{10}}$
	-COOH	1.20	1.25	0.05
	 $-\overset{O}{\overset{\Vert}{C}}-OCH_3$	1.20	1.26	0.06
	 $-\overset{O}{\overset{\Vert}{C}}-\overset{H}{\overset{\vert}{N}}-CH_3$	1.20	1.29	0.09
	 $-\overset{O}{\overset{\Vert}{C}}-N(CH_3)_2$	1.25	1.39	0.14

the methyl groups ($\Delta\delta_{C_4 - C_{10}}$) were observed when the functional group was β at C-4 and particularly so when the naphthyl ring was involved (shielding effect of the ring current when positioned favourably over the C-10 methyl). When the functional groups were α at C-4 (dehydroabietyl series), the magnitude of the chemical shift differences were rather small.

The investigation was then extended to include the sodium trimesitylboron radical anion as a reducing agent toward the same esters.

Reduction with Sodium Trimesitylboron.

Methyl mesitoate was employed as substrate for initial investigation due to its failure upon reduction with both NaNp and NaHMPA to give clear results. The effects of varying the ratio of reactants on the formation of products are given in Table VI (see entries 1 to 4). In the absence of the proton source, t-BuOH, three products were isolated - the acid (50%) and the two coupling-type products observed previously in reactions with NaNp, namely, mesitil (35%) and mesitoin (11%). The formation of the latter products was eliminated when t-BuOH (added just prior to the addition of the ester) was present in the reducing solution (Table VI, entries 2 - 4). Excellent

TABLE VI

Reactions of Hindered Esters with Sodium Trimesityboron in Tetrahydrofuran at 25°C

Entry	Ester	Molar Ratio of Reactants				Reaction Time	Products (% yield)	
		Na	TMB	*t*-BuOH	ester	(hr)	ester	acid
1.	**3a**	3.6	2.3	--	1.0	15	0	50[a]
2.	**3a**	6.3	2.1	2.1	1.0	4	0	66[b,c]
3.	**3a**	5.0	2.0	3.0	1.0	6.5	0	80[b,c]
4.	**3a**	2.2	2.0	1.5	1.0	1	30 - 35	41[c]
5.	**1a**	5.4	2.1	3.0	1.0	10	76	21
6.	**1a**	6.3	2.2	--	1.0	0.5	100	0
7.	**4g**	*ca* 4.0	2.1	--	1.0	0.5	100	0
8.	**4g**	5.6	2.1	3.0	1.0	10	100	0

(a) Mesitil (35%) and Mesitoin (11%) were also isolated.

(b) An unidentified clear viscous liquid also isolated (10 - 15%).

(c) The presence of *t*-BuOH prevented the formation of mesitil and mesitoin.

results (80% yield of acid) were obtained when excess sodium and *t*-BuOH were employed (entry 3).

Conditions incorporating the most favourable ratio of reactants were then applied to the equatorial resin ester, **1a**. The starting ester (76% yield) was recovered along with 21% of the corresponding acid, **1c**. The axial ester, **4g**, did not react with NaTMB under these conditions and was completely recovered unchanged. When the reaction was repeated with both resin esters, **1a** and **4g**, in the absence of *t*-butyl alcohol, no reduction occurred, and both starting materials were recovered quantitatively. Thus $Na^{+}TMB^{\bar{\cdot}}$ reacts either extremely slowly with the resin esters or not at all.

In conclusion, the reaction of sterically hindered esters with radical anions was shown to be a complex process. In no case was the corresponding alcohols of the types observed by Wenkert and Jackson ever obtained. Thus, the radical anions investigated here do not appear to simulate the reactivity and selectivity displayed by metal in liquid ammonia solutions. Rather, some unexpected and novel products were obtained.

Whereas NaHMPA proved to be a species of very high reactivity, in contrast, the use of NaTMB may show some promise as a rather selective electron transfer reagent.

Since the completion of this work, L. St-Laurent has demonstrated its use as a selective electron transfer reagent for reductive cyclizations.[3] NaTMB had the added advantages of not acting as an alkylating agent, or undergoing no decomposition and of being totally recoverable. The order of reactivity (i.e., reducing ability) towards these hindered esters thus appears to be NaHMPA $\gg$ NaNp $\gg$ NaTMB.

Parameters such as temperature, mode of and time for addition, time for mixing, stoichiometry and the presence or absence of a proton source all play a role in affecting product distribution, some most dramatically.

EXPERIMENTAL

General Considerations

Infrared (ir) spectra recorded using a Perkin-Elmer 421 G or Unicam SP 200 Infrared Spectrophotometer. Ultraviolet (uv) spectra were determined using a Perkin-Elmer Model 202 Spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 or HR-100 Spectrometer. Unless otherwise stated, deutrochloroform ($CDCl_3$) was employed as the solvent with tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in δ values relative to TMS=0. The following abbreviations are used in the text: s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet.

Mass spectra were recorded on an AEI Model MS-2, Model MS-9 or MS-12 Spectrometer. Spectra are recorded in the following manner: *m/e*: peak mass (relative intensity).

Refractive indices were measured on a Bousch and Lomb Abbe-3L Refractometer.

Melting points were determined using a Fisher-Johns or a Reichert melting point apparatus and are uncorrected.

Microanalyses were performed by the Microanalytical Laboratory, University of Alberta.

All reactions involving the radical anion solutions were carried out using oxygen-free nitrogen[125,126] or argon.

Preparation of the Sterically Hindered Esters

A. Methyl Dehydroabietate

Pure dehydroabietic acid, mp 169-171.5°C, was obtained by treatment of the commercial grade product with 2-ethanolamine, acidifying the resulting pure ethanolamine salt with 3N HCl, followed by recrystallization of the acid from 75% alcohol according to the method of Halbrook and Lawrence.[127] The acid was then esterified with ethereal diazomethane[128] and the resulting methyl ester was chromatographed over BDH alumina using ligroine (bp 63-75°C) as eluent. This afforded colourless crystals of methyl dehydroabietate, mp 60-62°C [lit[129] 61-62.5°C]; ir (KBr disc): 1720 ($-\underline{C}O-OCH_3$), 1245 (axial ester[138]), 1170, 1120 ($-CO-\underline{O}-CH_3$) and 818 cm^{-1} (two adjacent H's on aromatic ring); nmr: δ 6.83 - 7.33 (m, 3, $Ar\underline{H}$), 3.66 (s, 3, $-CO-OC\underline{H_3}$), 2.62 - 3.08 (m, 3, $-C\underline{H_2}-C=C$), 2.1 - 2.45 (m, 1, $-C-\underline{H}$), 1.35 - 2.10 (m, 8, $-C\underline{H_2}-$), 1.27 (s, 3, $-C\underline{H_3}$ at C_4), 1.21 (d, 6, $-CH(C\underline{H_3})_2$, J=7cps) and 1.20 (s, 3, $-C\underline{H_3}$ at C_{10}); mass spectrum: $\underline{m}/\underline{e}$: 314(23), 299(25), 240(24), 239(100) and 173(8).

B. Methyl O-methylpodocarpate

This material was prepared according to the procedure of Sherwood and Short[131] by treating a 50% aqueous ethanolic solution of podocarpic acid (1.0 equiv.) containing sodium hydroxide (3.2 equiv.) with dimethyl sulfate (3.0 equiv.), mp 126-128°C [lit[131] 128°]; ir (CS_2): 1721 ($-\underline{C}O-OCH_3$), 1185, 1145 cm^{-1} (equatorial ester[130]); nmr: δ 6.5 - 6.9 (m, 3, ArH), 3.72 (s, 3, $Ar-OC\underline{H}_3$), 3.63 (s, 3, $-CO-OC\underline{H}_3$), 1.3 - 2.9 (m, 11, aliphatic H's), 1.24 (s, 3, $-CH_3$ at C_4) and 1.02 (s, 3, $-CH_3$ at C_{10}); mass spectrum: *m/e*: 302(70), 287(5), 255(5), 243(5), 228(20), 227(100), 173(19), 171(22), 161(19) and 147(19).

C. Methyl mesitoate

2,4,6-Trimethylbenzoic acid was esterified with diazomethane (or dimethyl sulfate) to afford the colourless liquid, methyl-2,4,6-trimethylbenzoate (methyl mesitoate), n_D^{19} = 1.5090 [lit[132] n_D^{20} = 1.5083]; nmr: δ 6.86 (s, 2, $Ar\underline{H}$), 3.86 (s, 3, $-CO-OC\underline{H}_3$) and 2.27 (s, 12, $Ar-C\underline{H}_3$).

Preparation of Sodium Naphthalene Solutions

Stock solutions of sodium naphthalene (0.3 - 0.55m) were prepared by stirring (with a glass-covered magnetic bar) sodium pellets (1/16" to 1/4" in diameter) with 1.1 molar equivalent of naphthalene in dry tetrahydrofuran, in a sealed system under an atmosphere of nitrogen at room temperature. Formation of the radical anion appeared to be sensitive to traces of oxygen or other impurities and the time required for complete reaction of the sodium under these conditions was quite variable. The active sodium content was determined by titration of 10 ml aliquots with 1.0N solution of absolute ethanol in benzene, to the disappearance of the green colour.[133]

General Procedure for the Reaction of Sterically Hindered Esters with Sodium Naphthalene in Tetrahydrofuran at 25°C (Table I).

Reaction between Methyl-O-methylpodocarpate (4g) and Sodium Naphthalene in Tetrahydrofuran (THF).

A solution of methyl-O-methylpodocarpate (1.80 g, 5.98 mmole) in 20 ml of anhydrous THF was added dropwise during 10 minutes to 2.3 molar equivalents of sodium naphthalene (25 ml, 0.55N) at 25°C. After stirring for an additional 60 minutes, the remaining sodium naphthalene was destroyed with 4 drops of aqueous THF (1:10 - H_2O:THF). Additional water was added. Then the mixture was acidified with concentrated HCl, and extracted with chloroform (three

25 ml portions). The combined organic extract was washed with 5% NaOH solution, brine, then dried over anhydrous sodium sulfate. Evaporation yielded 3.16 g of neutral products.

The basic extract was acidified with conc. HCl, extracted with $CHCl_3$ and dried ($NaSO_4$). Removal of solvent afforded 0.584 g (34% yield) of O-methylpodocarpic acid, mp 157-158°C [lit[105] 157-158°C].

The neutral residue was chromatographed over BDH alumina (Act. 2, pH 5), using Skelly "B", then benzene, then benzene-chloroform as eluents. In order of elution: naphthalene, a viscous liquid (0.32 g) and a white solid (0.57 g, 24%) were obtained. The latter solid was crystallized from acetone-$CHCl_3$ to yield a white solid, mp 245.5 - 246.5°C, which was identified as O-methylpodocarpyl 2-naphthyl carbinol (5). Ir (KBr disc): 3540 (-OH), 1608, 1570, 1120 and 1040 cm^{-1} (Ar-OCH_3); nmr (pyridine-d_5): δ 8.19 (s, 1, H_1), 7.85 (m, 3), 7.46 (m, 3) [7 naphthyl protons], 6.80 (m, 3, H of benzene ring), 6.42 (broad s, 1, -OH, exch by D_2O), 5.72 (d, 1, -CHOH-, J=2Hz, s on exch by D_2O), 3.66 (s, 3, Ar-OCH_3), 1.2 - 2.95 (m, 11, aliphatic H's), 1.56 (s, 3, -CH_3 at C_4) and 1.07 (s, 3, -CH_3 at C_{10}); mass spectrum: *m*/*e*: (calcd. for $C_{28}H_{32}O_2$: 400.2402. Found: 400.2349.): 400(5), 272(5), 244(52), 173(30), 161(100), and 156(28); uv max (absol. EtOH) 228.5 (ε = 73,00), 279 (ε = 5,750), 289 mμ (ε = 4,080). Anal. Calcd. for $C_{28}H_{32}O_2$: C, 83.96; H, 8.05; O, 7.99. Found: C, 83.14; H, 7.93.

Inverse addition

To a solution of 4g (1.82 g; 6.03 mmole) in 20 ml of THF at 25°C was added dropwise (10 min.) 25 ml of a 0.55N sodium naphthalene solution (2.3 equiv.). After addition the solution was stirred for an additional 60 minutes, then quenched with aqueous THF and extracted as described previously. Acid (4f), 0.59 g (34%) was isolated; the neutral products were not investigated.

Reaction between Methyl-O-methylpodocarpate and 6.6 equivalents of Sodium Naphthalene.

Using the same procedure as described above, with the exception that 6.6 equiv. of sodium naphthalene was used, 1.897 g (6.28 mmole) of the ester (4g) yielded after workup 0.310 g (17.5%) of the acid (4f) in addition to neutral products. The naphthalene was removed by elution of the neutral products on BDH alumina with pet ether. Elution with pet ether, pet ether-benzene and benzene gave 1.31 g (54.4%) of 4i. Further elution with $CHCl_3$ afforded 0.39 g (15.5%) of O-methylpodocarpyl 2-naphthyl carbinol (5) and

0.45 g of an unidentified viscous liquid. Compound 4i, a white crystalline solid, mp 140-141°C (Skelly "B"), was shown to be O-methylpodocarpyl 2-naphthyl methane (9). Ir (KBr disc): 1605, 1495, 1035 (Ar-O-CH_3), 790 and 775 cm^{-1}; nmr ($CDCl_3$): δ 8.18 (d of d, 1, H_3 or H_1), 7.77 (m, 2), 7.41 (m, 4) [7 naphthyl protons], 6.83 (m, 3, ArH, ABC system) [7.00 (d, 1, H_B, J_{BC} = 9Hz), 6.88 (d, 1, H_A, J_{AC} = 2.5Hz), 6.67 (d of d, 1, H_C, J_{AC} = 2.5Hz, J_{BC} = 9Hz)], 3.76 (s, 3, ArOC$\underline{H}_3$), 3.21 (s, 2, naph-CH_2-), 2.92 (m, 2, Ar-C$\underline{H}_2$-), 1.34 to 2.54 (m, 9), 1.41 (s, 3, -C$\underline{H}_3$ at C_4), and 0.65 (s, 3, -C$\underline{H}_3$ at C_{10}); nmr (pyridine-d_5): δ 8.34 (d, 1, H_3 or H_1, J 8Hz), 7.88 (m, 2), 7.50 (m, 4) [7 naphthyl protons], 6.98 (m, 3, Ar$\underline{H}$), 3.76 (s, 3, Ar-OC$\underline{H}_3$), 3.23 (s, 2, naph-C$\underline{H}_2$-), 2.90 (m, 2, Ar-C$\underline{H}_2$-), 1.2 - 2.5 (m, 9), 1.38 (s, 3, -C$\underline{H}_3$ at C_4) and 0.62 (s, 3, -C$\underline{H}_3$ at C_{10}); mass spectrum: m/e: (Calcd. for $C_{28}H_{32}O$: 384.2453. Found: 384.2444): 384(15), 243(15), 173(25), 161(100), 147(23) and 141(25). Anal. Calcd. for $C_{28}H_{32}O$: C, 87.45; H, 8.39 Found: C, 86.62; H, 8.48.

Reaction between Methyl Dehydroabietate (1a) and Sodium Naphthalene.

In the same manner as described earlier, employing 2.8 equiv. of sodium naphthalene 1.560 g (4.97 mmole) of the equatorial ester yielded after workup 0.070 g (4%) of the acid (**1c**) and 3.48 g of neutral products. Column chromatography on BDH alumina gave, in addition to naphthalene, three major fractions: from Skelly "B"-benzene (1:1) elution, 0.55 g; from benzene, 0.40 g and from $CHCl_3$, 0.67 g. The first and third fractions were shown (tlc) to contain at least six components. Further attempts at separation by additional column chromatography and prep. tlc proved fruitless. Attempts at structure elucidation of the mixture using spectral methods failed to provide any definitive evidence.

Reaction between Methyl Mesitoate (**3a**) and Sodium Naphthalene.

A solution of 0.895 g (5 mmole) of **3a** in 25 ml of THF was added dropwise (15 min.) to 25 ml of 0.40N sodium naphthalene reagent (2.0 equiv.). After addition was complete, the initial green-black colour turned brown-black. The mixture was stirred an additional 45 minutes, then quenched with aqueous THF. Workup in the usual manner yielded 0.047 g (5%) of acid, and 1.99 g of neutral products.

The acid, mp 151-153°C [lit[107] 153-154°C], showed an nmr spectrum identical to that of authentic mesitoic acid: δ 6.84 (s, 2, ArH), 2.39 (s, 6, $-CH_3$ at C_2 and C_6), and 2.26 (s, 3, $-CH_3$ at C_4).

Column chromatography removed the naphthalene and afforded 0.59 g of a mixture, shown (tlc, silica gel HF_{254}) to contain at least five components. Elution on alumina with Skelly "B"-benzene (50:50) gave 0.25 g (34%) of a yellow crystalline solid, mesitil, mp = 118.5 - 119.5 [lit^{134} 119-120°C]. Ir ($CHCl_3$, 1%, 0.5 mm): 1695 (Ar-CO-CO-Ar), 1610, and 850 cm^{-1}; mass spectrum: *m/e*: 147 (Mes-CO)$^{+\cdot}$ and 119 (Mes)$^{+\cdot}$; nmr: δ 6.84 (s, e, Ar$\underline{H}$), 2.29 (s, 6, -C$\underline{H}_3$ on C_4 and $C_{4'}$) and 2.20 (s, 12, -C$\underline{H}_3$). Elution with methanol gave 90 mg (16%) of a yellow viscous liquid, shown to be mesitoin. Ir ($CHCl_3$), 3530 (-OH), 1680 (-C=O), 1590, 1035, and 850 cm^{-1}; nmr: δ 6.70 (m, 4, ArH), 5.24 (s, 1, -C$\underline{H}$OH-), 3.23 (broad s, 1, -CHO$\underline{H}$-, exch with D_2O) and 1.8 to 2.4 (m of s, 18, 9-C$\underline{H}_3$).

It was shown, on the basis of nmr spectra, that none of the remaining unidentified compounds contained the presence of a naphthyl moiety.

Reaction between Methyl O-methylpodocarpate (4) with excess Sodium Naphthalene in the Presence of t-Butyl alcohol.

To 3.987 g (31.1 mmole) of naphthalene in 50 ml of anhydrous THF was added 0.21 g (9.1 mg-atom) of sodium. The resulting dark green solution was stirred 2 hours, then cooled to 0°C. A solution of 0.428 g (5.77 mmole) of t-butyl alcohol in 10 ml of THF was added all at once and the mixture was stirred for two minutes. Then 0.454 g (1.50 mmole) of the ester (4g) in 20 ml of THF was added (15 min.) The mixture was stirred at 0°C for a further 30 minutes then quenched with 1N HCl.

Workup as described previously gave 0.445 g (98%) of starting material 4g.

Oxidation of O-methylpodocarpyl 2-naphthyl carbinol (5) to O-methylpodocarpyl 2-naphthyl ketone (8).[115]

A solution of 300 mg (0.75 mmole) of the alcohol (5) in 6 ml of anhydrous pyridine was added to a slurry of 450 mg (4.5 mmole) of CrO_3 in 6 ml of anhydrous pyridine at 25°C. After addition, the mixture turned dark brown within a few minutes. The mixture was stirred at 25°C (N_2, 11 hr), then filtered. Water (50 ml) and chloroform (100 ml) were added to the filtrate and the mixture was washed with 5% HCl, saturated bicarbonate solution, brine, dried (Na_2SO_4) and evaporated to leave 456 mg of a brown material.

Elution of this material on a column of BDH alumina with ligroine (63-75°C) and subsequent recrystallization from methanol gave 72 mg of white crystals of ketone 8 mp 160-162.5°C. Ir (KBr disc): 1670, 1625, 1608, 1571, 1500, 1247 and 1035 cm^{-1}; nmr (pyridine-d_5): δ 8.23 (s, 1, H_1), 7.84 (m, 3), 7.48 (m, 3) [7 naphthyl protons], 6.85 (m, 3, Ar$\underline{H}$), 3.60 (s, 3, Ar-OCH_3), 1.9 - 2.9 (m, 7, aliphatic H's), 1.1 - 1.6 (m, 4, aliphatic H's), 1.44 (s, 3, -$C\underline{H_3}$ at C_4) and 1.19 (s, 3, -$C\underline{H_3}$ at C_{10}); nmr ($CDCl_3$): δ 8.05 (s, 1, H_1), 7.89 (d, 1, H_3, J=8Hz), 7.83 (m, 2), 7.57 (m, 3) [7 naphthyl protons], 6.81 (m, 3, Ar$\underline{H}$), 3.77 (s, 3, Ar-$OC\underline{H_3}$), 1.63 (s, 3, -$C\underline{H_3}$ at C_4) and 1.24 (s, 3, -$C\underline{H_3}$ at C_{10}); nmr ($CDCl_3$ + ca 0.5 equiv. of Eu(fod)$_3$): δ 10.09 (s, 1, H_1) and 9.93 (d, 1, H_3, J=8Hz). Mass spectrum: m/e (Calcd for $C_{28}H_{32}O_2$: 398.2246. Found: 398.2258): 398(35), 243(12), 173(24), 161(100), 155(70) and 127(23); uv max ($CHCl_3$-EtOH (1:9)) 242 (ε = 51,400) shoulder at 250, 281 mμ (ε = 15,700) with shoulder at 288 mμ.

Reduction of Benzil to Benzoin by Sodium Naphthalene.

A 0.9N stock solution of NaNp in DME containing 10% toluene was available in our laboratory and was used for the above reduction.

A solution of 4.33 g of benzil in 50 ml of THF was added dropwise (10 min.) to two equivalents of the NaNp solution. After an additional 60 minutes of stirring, the mixture was quenched with aq. HCl - THF solution. The solvent was evaporated, and benzene was added in order to azeotropically remove the trace amount of water. The residue was washed with pet ether to remove the naphthalene. The remaining white solid was crystallized from ethanol to give 3.22 g (75%) of benzoin, mp 134-135°C [lit[135] 135°C]. The ir and nmr spectra were identical to those of an authentic sample. The lower limit of the yield is 75% but additional unisolated material was shown to be present in the pet ether washings (tlc, silica gel, benzene: $CHCl_3$ - 80:20); no starting material was present (tlc).

Preparation of Sodium Hexamethylphosphoramide

Hexamethylphosphoramide (HMPA) was first dried over 13X molecular sieves, then distilled from sodium (2.0 g/ 500 ml) to give a colourless liquid, bp 65°C/0.5 mm; 75-76°C/2 mm [lit[55] 65°C/0.4 mm, [5] 68-70°C/1.0 mm]

The THF was purified by shaking with successive portions of sodium hydroxide pellets, refluxing for 24 hours over sodium spheres, then distilling from sodium metal. The distilled THF was then treated with $LiAlH_4$ and redistilled under a nitrogen atmosphere prior to use. [WARNING: It has been reported that serious explosions may occur when impure THF is treated with solid potassium hydroxide.[136]]

Stock solutions of NaHMPA (0.2 - 0.3M in Na) were prepared by adding ca 1.0 g of freshly cut sodium spheres (1/16" to 1/4" in diameter) to 60 ml of stirred (glass-covered magnetic bar) HMPA under nitrogen for one minute and then diluting with 30 ml of THF [N.B. House's preparation[55] should possibly read 1.0 g instead of 10 g]. The resulting mixture was stirred at 0° for 2 to 5 hours and standardized (as described for sodium naphthalene, p. 50) before use.

All solutions of NaHMPA-THF used were in the ratio 2:1 in HMPA:THF, unless otherwise specified.

Reaction between Methyl-O-methylpodocarpate (4g) and NaHMPA-THF at 25°C.

A solution of 4g (0.83 g, 2.75 mmole) in 25 ml of HMPA-THF (2:1) was added dropwise over 55 minutes to 40 ml of ca 0.2M NaHMPA-THF. During addition, the reaction was exothermic and a gas was evolved. After complete addition of the ester, the blue colour remained. The solution was stirred an additional 5 minutes, then quenched with methanol.

The mixture was concentrated on a rotavapor and the remaining solution was partitioned between 5% HCl and $CHCl_3$. (In the initial experiments, $CHCl_3$ was used.

Subsequently, Skelly "B" was used as the solvent for extraction due to the ability of chloroform to form complexes with HMPA.[55]) The combined chloroform extract was washed with 5% NaOH solution (four 40 ml portions), water (100 ml), brine (100 ml), then dried (Na_2SO_4). Evaporation afforded the neutral products which still contained HMPA. In order to remove the HMPA the extraction was repeated with Skelly "B". This eventually afforded 50 mg (6.3%) of a compound with a molecular weight of 287 (mass spectrum).

The sodium hydroxide washings were acidified (conc. HCl), then extracted with $CHCl_3$. The combined organic extracts were shaken with brine (100 ml), dried (Na_2SO_4), and evaporated to yield 0.625 g of an off-white solid, mp 115-127°C. Recrystallization from aq. methanol yielded the colourless crystalline podocarpic : HMPA 1 : 1 complex (13), mp 154-156°C, and a viscous liquid. Further crystallization (aq. ethanol) of the viscous liquid yielded podocarpic acid, mp 190-192°C [lit[131] 193.5].

Spectral data for 13: mass spectrum: m/e: 274, 259, 213, 179, 157, 136, and 135. The 179, 136 and 135 peak were characteristic of HMPA; the remaining features of the spectrum were identical to that observed for authentic podocarpic acid. Nmr (pyridine-d_5, 100 MHz): δ 7.16 (s, 1, ArH), 6.99 (s, 2, ArH), 2.8 (m, 2, Ar-CH_2-), 2.5 (d, 18, CH_3's of HMPA, J=10Hz), 2.0 - 2.6 (m, 5) and 1.15 to 1.75 (m, 10).

Reaction between Methyl Dehydroabietate (1a) and NaHMPA-THF at 25°C.

In a similar manner to that described above for 4g, to 25 ml of a 0.2M NaHMPA-THF solution (3.5 equiv.), a solution of 1a (0.504 g, 1.67 mmole) in 20 ml of THF was added dropwise over 25 minutes. Five minutes after addition, the reaction was quenched with aqueous THF. Workup as before (with Skelly "B" instead of $CHCl_3$ as the extracting solvent), yielded 0.21 g (44%) of dehydroabietic acid, ir and nmr identical to an authentic sample, and 0.26 g of neutral products. Trituration of the neutral product with Skelly "B" and recrystallization (Skelly "B"-ether) afforded 0.18 g (36%) of N-methyldehydrobietamide as a white crystalline solid, mp 165-165.5°C [lit[137] 156.5-158.3]; ir ($CHCl_3$, 2%, 0.5mm): 3490 (amide N-H), 1650 (amide C=O) and 1385 cm^{-1} ($-C(CH_3)_2$); mass spectrum: *m/e* 313(100), 298(65), 239(65), 173(61) and 159(27); nmr ($CDCl_3$, 100 MHz): δ 6.97 (m, 3, ArH), 5.87 (broad s, 1, NH), 2.75 (d, 3, $N-CH_3$, J=5Hz), 2.75 (m, 3, $Ar-CH_2-$), 2.25 (m, 1), 1.60 (m, 8) and 1.21 (s, 3, $-CH_3$ at C_4), 1.17 (d, 6, isopropyl methyls, J=7ps) and 1.17 (s, 3, $-CH_3$ at C_{10}).

When a slower addition rate (80 minutes) was employed for this reaction, a decrease in acid (5%) and an increase in amide (ca 66%) was observed.

Reduction of the Hindered Esters with NaHMPA-THF at 0°C: General Procedure (see Table III):

To a solution of NaHMPA-THF at 0°C under an atmosphere of nitrogen or argon was rapidly added (0.5 min.) a solution of the ester in 15 ml of anhydrous THF. The resulting solution (deep blue colour) was stirred for 5 minutes, quenched with aqueous THF, then poured into 150 ml of 1N HCl. Extraction with ether (three 25 ml portions) was followed by washing the combined ether extracts with 5% NaOH (three 25 ml portions).

The resulting ether layer was shaken with brine (50 ml) and dried (Na_2SO_4). Evaporation of the solvent yielded the neutral fraction.

The solid acidic products were obtained from the 5% NaOH extracts by reprecipitation with conc. HCl and filtration.

With Methyl-O-methylpodocarpate (4g).

As outlined above in the general procedure, 4g (0.54 g, 1.79 mmole) was added to 7.4 mmole of NaHMPA-THF (4.1 equiv.). This reaction gave as products, 0.456 g

(88.6%) of O-methylpodocarpic acid (4f), mp 154-158°C (Skelly "B") [lit[105] 158-161°C, [107] 157.5-158.5°C], nmr and mass spectrum identical to an authentic sample, and 65 mg (8%) of N-methyl-O-methylpodocarpamide (4j), mp 91-93°C (Skelly "B").

Spectral data for 4j include: ir ($CHCl_3$, 2%, 0.5mm): 3490 (amide N-H) and 1650 cm^{-1} (amide C=O); mass spectrum: *m/e* (Cacld. for $C_{19}H_{27}NO_2$: 301.2043. Found: 301.2038): 301(50), 286(7), 270(16), 229(25), 228(100), 227(18), 173(16), 171(15) and 161(21); nmr: δ 6.84 (m, 3, ArH), 5.74 (bd s, 1, NH, exch with D_2O), 3.81 (s, 3, OCH_3), 2.85 (m, 2, Ar-CH_2-), 2.85 (d, 3, -NCH_3, J=5Hz), 1.40 to 2.44 (m, 9), 1.32 (s, 3, -CH_3 at C_4) and 1.18 (s, 3, -CH_3 at C_{10}).

With Methyl-O-methylpodocarpate (4g) in the Presence of t-Butyl alcohol.

As in the general procedure, 4g (0.54 g, 1.78 mmole) was added to a solution of 13.3 mmole of NaHMPA-THF (7.47 equiv.) and 0.366 g (4.94 mmole, 2.76 equiv.) of *t*-butyl alcohol. The *t*-BuOH was added to the radical anion solution prior (1 min.) to addition of the ester. This reaction afforded 0.378 g (73.4%) of 4f and 0.127 g (23.5%) of 4j.

With Methyldehydroabietate (1a).

As in the general procedure, 1a (0.56 g, 1.78 mmole) was added to 20 ml of a 0.24M NaHMPA-THF solution (4.8 mmole, 2.7 equiv.). The neutral fraction was shown (tlc) to contain at least six components. N-Methyldehydroabietamide (1d) was isolated (10 mg, 2 - 4%) by preparative tlc and its ir spectrum ($CHCl_3$) was identical to that of an authentic sample. The remaining neutral components were not identified.

Addition of conc. HCl to the NaOH extracts, followed by refrigeration overnight, failed to precipitate the acid (1c). Extraction with ether - Skelly "B" gave 16 mg of 1c. Additional acid was obtained by the addition of NaCl and further addition of conc. HCl. Extraction with ether - Skelly "B" yielded 0.428 g of a viscous liquid whose nmr spectrum ($CDCl_3$) was indicative of the dehydroabietic acid:HMPA complex: δ 2.62 (d, J=9Hz, HMPA) plus dehydroabietic acid pattern. The viscous liquid was diluted with 40 ml of THF, 1 ml of acetic acid was added and the resulting solution was refluxed for one hour. The THF was removed by evaporation (rotavapor), and the residue was partitioned between Skelly "B" and water. The organic layer was dried (Na_2SO_4) to provide, after removal of the solvent, 0.269 g of 1c, mp 154 - 165°C, 159 - 169°C (recry 75% EtOH); nmr ($CDCl_3$) identical to that of an authentic sample.

With Methyldehydroabietate (1a). Inverse addition.

To the ester (0.508 g, 1.61 mmole) in 15 ml of THF at 0° was added, by means of a hypodermic syringe, 20 ml of a 0.2N NaHMPA-THF solution (4.0 mmole, 2.5 equiv.) over 15 seconds. The resulting solution was stirred 5 minutes, then quenched with 1N HCl. Workup gave 0.34 g (70.2%) of 1c and 0.105 g of neutral products.

The neutral residue was shown (tlc) to contain at least five components. One tlc spot was coincident with an authentic sample of N-methyldehydroabietamide (1d).

With Methyl Mesitoate (3a).

As outlined in the general procedure, 3a (0.365 g, 2.05 mmole) was added to 20 ml of a 0.24M NaHMPA-THF solution (4.8 mmole, 2.34 equiv.). Workup as previously described gave 0.138 g of an acidic fraction, shown by tlc [Polygram, Sil G/uv, $CHCl_3$:EtOAc:HOAc (50:50:1)] to contain four spots, and 0.226 g of a neutral fraction shown by tlc [Polygram, Sil G/uv, benzene:Skelly"B" (1:1)] to contain three compounds. Column chromatography (BDH alumina) of the neutral fraction gave 40 mg (13.3%) of mesitil on elution with Skelly "B"-ether (9:1) whose ir spectrum was identical to that of an authentic sample. In view of the complexity of the reaction, no further attempts were made to elucidate the structures of the remaining compounds.

With Methyl Mesitoate (3a) in the Presence of t-Butyl Alcohol.

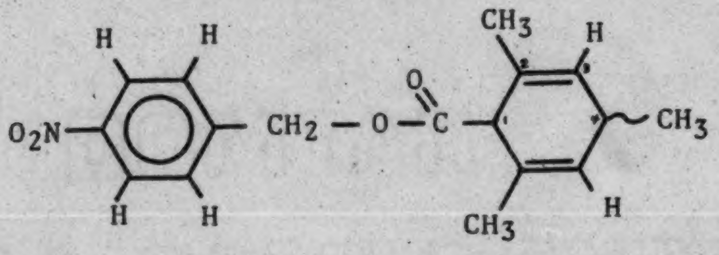
In a similar manner as above, 3a (0.360 g, 2.02 mmole) was added to 40 ml of a 0.24M NaHMPA-THF solution (9.6 mmole, 4.7 equiv.) and 0.228 g (3.08 mmole, 1.5 equiv.) of t-butyl alcohol. The proton source was added to the radical anion one minute prior to addition of the ester.

Workup yielded the same seven products as in the previous reaction but in different ratios (by intensity of tlc spots).

The nmr spectrum of the acid fraction (83 mg, 4 components by tlc, one major spot) exhibited absorption at: δ 0.98 (d, 3, $-CH_3$, J=7Hz), 1.02 (d, 3, $-CH_3$, J=7Hz), 1.78 (s, 12, $-CH_3$), 2.83 (broad m, 2, -CH-COOH), 3.38 (s, 1, allylic H), 3.48 (s, 1, allylic), 5.62 (2s, 4, vinyl H) and 10.27 (broad s, 2, -COOH, exch by D_2O). The above nmr spectrum is consistent with a mixture of epimeric acids with the 1,4-dihydromesitoic skeleton 15.

In an effort to further confirm the structures of the epimeric acids (14), the p-nitrotoluyl ester derivatives were prepared as outlined in Shriner, Fuson and Curtin.[138] Elution with benzene over Al_2O_3 of the product from the derivatization reaction gave 125 mg of a viscous liquid which failed to crystallize; nmr (see structure 15): δ 0.90 and 1.18 (d, 3, $-CH_3$ at C_4, J=7Hz), 2.24 (s, 6,

-C$\underline{H}_3$ on C_2 and C_6), 3.56 (q, 1, H at C_4, J=7Hz), 4.48 (s, 2, O_2N-Ar-C$\underline{H}_2$-), 4.57 (s, 1, H at C-1), 5.21 (s, 1, H at C-3), 5.40 (s, 1, H at C-5), 7.60 (m, 2, Ar$\underline{H}$) and 8.20 (m, 2, Ar$\underline{H}$) in addition absorptions at 1.67 (s) 5.53 (bd s) and 6.85 (s) were observed. Further elucidation was abandoned.



15

Reaction of Dehydroabietic Acid with NaHMPA-THF

To 0.570 g (1.9 mmole) of 1a in 15 ml of THF at 0°C was added, by means of a hypodermic syringe, 20 ml of a 0.2N NaHMPA-THF solution (4.0 mmole, 2.1 equiv.). The resulting solution was stirred (0°, 30 min.), then quenched with 1N HCl. Workup in the usual manner gave a white solid mp > 320°C, thought to be the sodium salt of 1a due to incomplete neutralization.

Addition of the solid to 50 ml of ether containing 1 ml of acetic aicd and a few drops of conc. HCl, yielded, after washing (25 ml H_2O), drying (Na_2SO_4), and evaporation of the ether, 0.570 g (100%) of the starting material, 1a, mp 165 - 170°C (75% EtOH) [lit[127] 171.5-172.5°C]. The nmr spectrum was identical to that of an authentic sample.

Preparation of N,N-dimethyldehydroabietamide (1e).[120]

To 2.348 g (7.8 mmole) of dehydroabietic acid (1a), 2 ml of thionyl chloride was added and the resulting solution was stirred at 25°C for 15 minutes. Then 2 drops of DMF was added and the mixture was stirred for a further 24 hours. Thereupon, DMF (12 ml) was added and the solution heated to reflux for 4 hours. The resulting black solution was partitioned between Skelly "B" and water. The organic layer was washed successively with water, 5% NaOH, water, dil. HCl, brine then dried ($MgSO_4$). Solvent was evaporated to yield 1.40 g of a dark brown viscous liquid: ir ($CHCl_3$) 1610 cm^{-1} (amide C=O).

Column chromatography with Skelly "B" over BDH alumina, followed by short path distillation (Kugelrohr, 180°C at 0.18 mm Hg) afforded 0.750 g (30.0%) of a viscous liquid: ir ($CHCl_3$) 1610 (amide C=O) and 1380 cm^{-1} (gem-dimethyl of isopropyl); mass spectrum: m/e: 327(35), 312(27), 255(26), 240(15), 239(65), 185(30) and

173(100); nmr: δ 7.0 (m, 3, ArH), 3.03 (s, 6, N-C$\underline{H}_3$), 1.5 to 3.10 (m, 12, aliphatic hydrogens characteristic of the dehydroabietyl skeleton), 1.36 (s, 3, -C$\underline{H}_3$ at C_4), 1.25 (s, 3, -C$\underline{H}_3$ at C_{10}) and 1.23 (d, 6, isopropyl-C$\underline{H}_3$, J=7Hz).

Reaction of N,N-dimethyldehydroabietamide (1e) with NaHMPA-THF.

A solution of the amide 1e (2.0 mmole), in 20 ml of THF was added (3 min.) to 20 ml of a 0.2N NaHMPA-THF solution (4.00 mmole) at 0°C. During addition the blue colour faded. Therefore an additional 10 ml of 0.2N NaHMPA-THF solution was added. The solution was stirred for a total of 30 minutes, then quenched with 1N HCl.

The resulting mixture was poured into 100 ml of 1N HCl and extracted with Skelly "B" (three 30 ml portions). The combined organic extract was washed with water (40 ml), brine (50 ml) and dried (Na_2SO_4). Evaporation of solvent yielded 0.567 g of a viscous liquid, shown by ir, nmr and tlc [Sil Gel G; benzene:EtOAc (1:1)] to be ca. a 50:50 mixture of the dimethyl (1e) and monomethyl (1d) amides. Elution BDH alumina with benzene: EtOAc (9:1) afforded ca 0.3 g of 1d, N-methyldehydroabietamide, mp 161 - 165.5°C, ir, nmr, mass spectrum and tlc behavior was identical to that of an authentic specimen.

Preparation of Trimesitylboron (TMB).

Trimesitylboron was prepared by the reaction of mesitylmagnesium bromide with boron trifluoride etherate according to the procedure of Brown and Dodson[6], with the following modification. During the preparation of the Grignard reagent, the magnesium turnings were covered with 80 ml of THF and 20 ml of diethyl ether instead of 100 ml of diethyl ether. The presence of THF resulted in an increase in yield of TMB from *ca* 30% to 54%.

After crystallization from 95% EtOH, the TMB was chromatographed over a short column of BDH alumina with Skelly "B". After removal of solvent, a white solid was isolated, mp 196.5 - 197°C [lit[6] 190.5-191.5°C,[139] 194-195°C]: mass spectrum, *m/e*: Calcd for $C_{27}H_{33}{}^{11}B$: 368.2675. Found 368.2681.

All samples of TMB were always sublimed (140°, 0.1 mm Hg) prior to use.

Reduction of Methyl Mesitoate (3a) with Sodium Trimesitylboron.

To 80 ml of THF in a three neck 200 ml flask under nitrogen was added 2.457 g (6.68 mmole, 2.3 equiv.) of TMB and 0.236 g (10.26 mg-atom, 3.6 equiv.) of sliced sodium spheres. Rapid stirring with a glass-coated magnetic bar produced a pervading blue solution after 15 minutes. When a deep blue-black colour was obtained after 2 hours of additional stirring, a solution of **3a** (0.508 g, 2.85 mmole) in THF (20 ml) was added over 15 minutes. The resulting solution was stirred at 25°C for an additional 15 hours.

Excess reagent (no sodium metal remained) was destroyed by addition of a dilute solution of HCl in THF, The mixture was poured onto 100 g of ice containing 25 ml of methanol, then acidified with conc. HCl. This precipitated the TMB which was recovered by filtration (for reuse). The solid was washed with cold methanol : water (1:1) and the product obtained weighed 2.100 g (85%), mp 196.8 - 197.0°C after sublimation.

The filtrate was concentrated (rotavapor). The resulting aqueous mixture was extracted with Skelly "B" and the combined organic layer was washed with 5% NaOH solution (four 30 ml portions).

The organic layer containing the neutral products was washed with water, brine, dried (Na_2SO_4) and evaporated to provide ca 0.49 g of a yellow solid.

The basic extracts were combined, acidified with conc. HCl, and then extracted with Skelly "B" (three 30 ml portions). The combined organic extract containing the acidic products was washed with water, then brine. After drying (Na_2SO_4) and evaporation of solvent there was obtained 0.235 g (50.2%) of mesitoic acid, mp 151 - 153°C (50% aq. EtOH) [lit[107] 153-154°C]. The nmr spectrum ($CDCl_3$) was identical to that of an authentic sample.

The neutral products were chromatographed over BDH alumina. Elution with hexane provided 265 mg of TMB, mp 195 - 196°C (96% total recovery). Benzene elution yielded 150 mg (35.5%) of mesitil, a yellow solid, mp 117 - 118°C (hexane) [lit[134] 119-120°C]; the ir, nmr, and mass spectra were identical to that of an authentic sample. Further elution with chloroform yielded 45 mg (10.6%) of mesitoin, whose ir, nmr and mass spectra proved identical to those of the previously isolated sample.

Reductions of Methyl Mesitoate (3a) with Sodium Trimesitylboron in the Presence of t-Butyl Alcohol.

Three reactions were carried out with t-butyl alcohol present as a proton source (Table VI, entries 2 to 4). The quantities of reactants for the three independent reactions were varied in the following amounts (mmole):

	Na	TMB	*t*-BuOH	ester
(1)	18.7	6.3	6.2	2.95
(2)	14.3	5.6	8.4	2.85
(3)	6.7	6.0	4.5	3.03

The procedures for these three reactions follow.

(1) The same procedure was used as described above for the reduction of methyl mesitoate with the exception that the *t*-butyl alcohol (2.31 g) was added dropwise (10 min.) together with the ester **3a** (0.525 g) in THF (20 ml) to the NaTMB solution. The resulting solution was stirred four hours at 25°C.

Workup (as above) gave 0.32 g (66.2%) of mesitoic acid, mp 153.5 - 154°C (crude). No evidence was obtained for the formation of any "coupling" products (i.e., mesitil or mesitoin). Column chromatography of the neutral fraction as before gave three products: TMB (from hexane eluate), 75 mg of an unidentified colourless viscous liquid (from benzene eluate), and by elution with chloroform, *ca* 140 mg of dimesitylborimic acid, mp 143.5 - 144°C (hexane) [lit[6] 140-141°C], ir ($CHCl_3$): 3600 (-OH), 1610, 1430, 1290, 1260, 1165, 1060, 856 and 812 cm^{-1}, nmr: δ 6.77 (s, 4, Ar$\underline{H}$), 5.88 (broad s, 1, -O$\underline{H}$)

and 2.25 (s, 18, -CH_3); mass spectrum: m/e: 266(5), 146(13), 122(10), 121(100), 120(20) and 105(16).

(2) As in (1) with the following modification: the t-butyl alcohol (0.625 g) in THF (15 ml) was added all at once to the radical anion solution two minutes prior to the addition (over 8 min.) of the ester (0.525 g) in THF (20 ml). The resultant solution was stirred 6.5 hours at 25°C.

Workup as before gave 1.98 g of TMB (95% recovery), mp 193 - 195°C; 0.374 g (80%) of mesitoic acid, mp 151 - 153°C, 90 mg of the same unidentified viscous liquid and ca 40 mg of dimesitylborimic acid.

(3) As in (2), however after one hour of stirring at 25°C, the blue colour of the radical anion was completely discharged. Therefore, the reaction was quenched and worked up to give 0.202 g (40.6%) of mesitoic acid, mp 154 - 155°C, and 33% methyl mesitoate (estimated by glc, 5 ft x 1/8" 5% SE 30 on chromosorb W at 123°C).

Reduction of Methyl Dehydroabietate (1a) with Sodium Trimesitylboron in the Presence of t-Butyl Alcohol.

The most favourable procedure and ratio of reactants in the above reductions of methyl mesitoate in the presence of t-butyl alcohol [reaction (2)] was chosen for the reduction of the resin ester, **1a**. Thus, 0.188 g-atoms (5.38 equiv.) of sodium was added to 1.135 g (2.08 equiv.) of the TMB in THF (80 ml) to form the radical anion. *t*-Butyl alcohol (0.333 g, 2.96 equiv.) was added as described previously, just prior to the addition (14 min.) of **1a** (0.477 g, 1.0 equiv.). The resulting solution was stirred 10 hours at 25°C before quenching.

Workup in a manner similar to the above gave 94 mg (20.6%) of the acid, **1c**, and 0.380 g (76%) of starting material, **1a**.

When a reduction was attempted with methyl-O-methylpodocarpate under identical conditions, complete recovery of the starting material was obtained.

Attempted Reductions of the Resin Esters with Sodium Trimesitylboron (Table VI).

Reductions were attempted with **1a** and **4g** in the same manner as outlined above in the absence of the proton source, *t*-butyl alcohol. No reduction occurred. The starting esters were both recovered quantitatively.

PART II

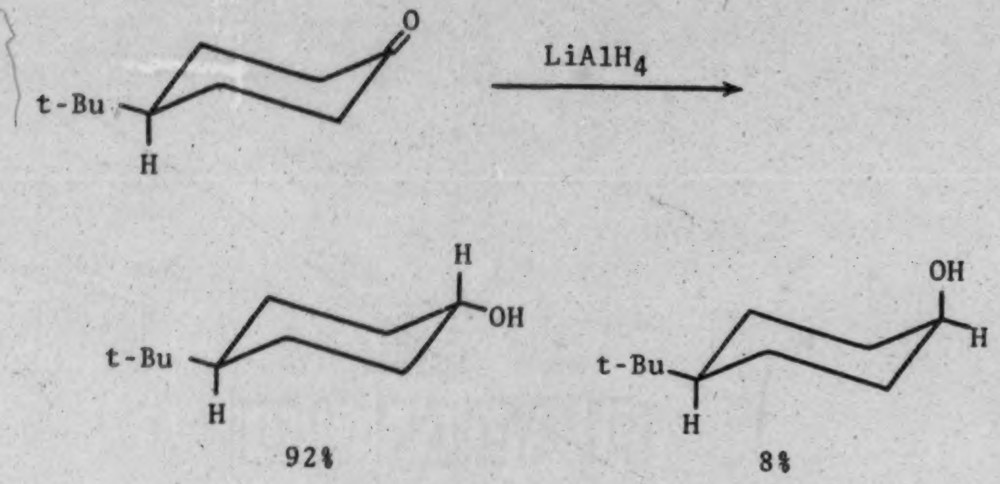
A STEREOSELECTIVE REDUCTION OF CYCLIC KETONES

INTRODUCTION

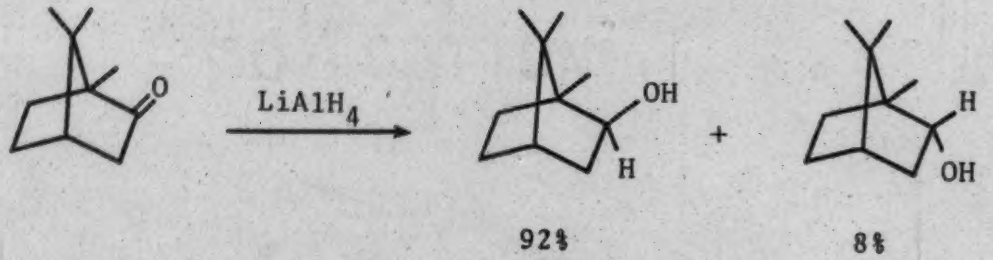
The stereoselective and stereospecific control of chemical reactions[140-142] is a topic of much concern to synthetic chemistry. In particular, the stereochemistry of addition of a variety of nucleophilic reagents to the carbonyl group has been the subject of numerous reports.[142-149]

Because the reductions of a large number of cyclic ketones with various reducing agents can lead to either epimeric alcohol as the major product, prediction of the stereochemical outcome of such reactions cannot always be made with certainty. This has generated a number of theories[145,150-155] to account for the observed results and considerable discussion.[145,151-160]

In reductions where the steric environment for the approach of the reducing agent to either side of the carbonyl function is comparable, as in 4-*t*-butylcyclohexanone, the major reduction product is usually the more stable product, i.e., the equatorial alcohol (eq. 25).[161] However, when approach to one side of the carbonyl function is definitely more hindered, as in camphor, the predominant formation of the least stable alcohol is favoured (eq. 26).[154]


O
t-Bu
H
LiAlH4
H
OH
t-Bu
H
92%
OH
H
t-Bu
H
8%

(25)

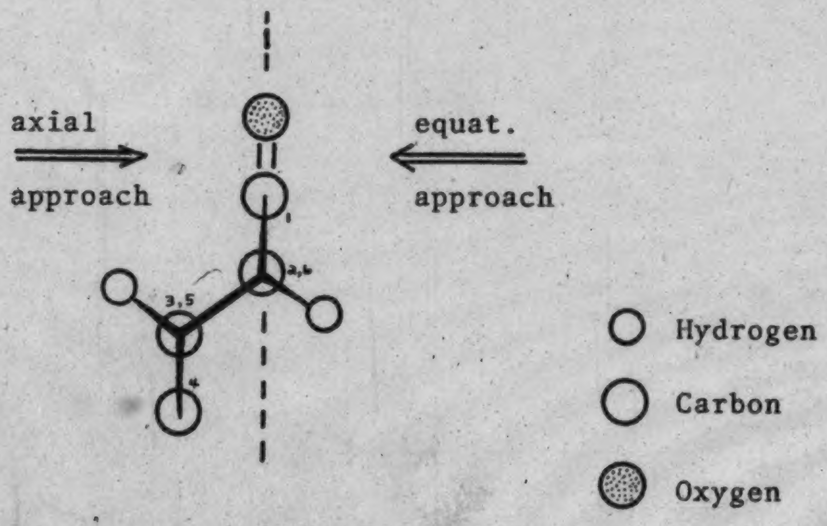

O
LiAlH4
OH
H
92%
+
H
OH
8%

(26)

In 1956, Dauben, Fonken, and Noyce termed these observations "product development control" and "steric approach control", respectively.[151] It was assumed that the transition state geometry resembled the geometry of the alcohol products for reduction of unhindered ketones, and resembled the starting ketone in geometry for the reduction of hindered ketones.

In 1965, Brown and Deck[154] suggested that the terms "steric approach control" and "product development control" be replaced by "steric strain control" and "product stability control" in order to focus greater attention on the transition state of the reaction rather than on events which occur on the way to the transition state.

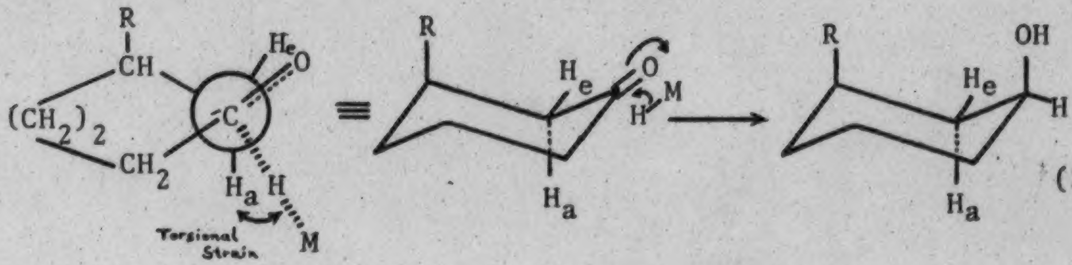
Also in 1965, an alternate explanation was suggested by Richer based on a "steric approach" only.[152] For a small entering group (which does not "interfere" with the 3,5-axial substituents), the reaction will be directed exclusively by the 2,6-axial substituents which hinder equatorial attack. However, as the size of the entering group becomes larger it was suggested that the interactions with 3,5-axial substituents increase and the reaction proceeds in favour of equatorial attack. This is most easily seen by envisaging



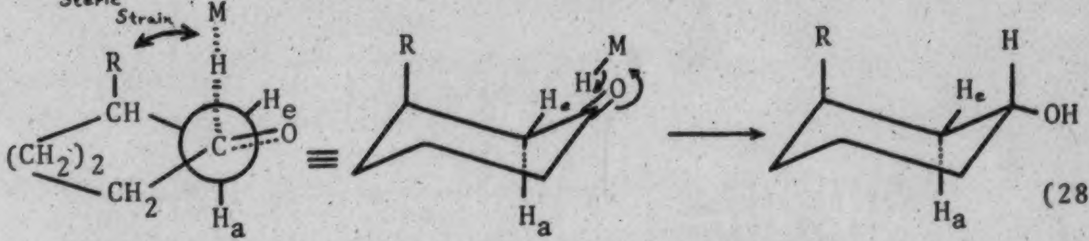
the approach of the nucleophile to an unhindered cyclohexanone perpendicular to the plane of the carbonyl group, not to the plane of the ring. The equatorial hydrogens (or other substituents) at the 2 and 3 positions are in the plane of the carbonyl group[162] and consequently will not interfere with a species approaching the carbonyl group from either the axial or equatorial side. On the other hand, the axial hydrogens are not in the plane of the carbonyl group (the 2,6-axial hydrogens are at an approximate angle of 116° with the carbonyl and the 3,5-axial hydrogens at an angle of *ca* 64°). and would interfere with a species approaching the carbonyl group from either side. Thus, the resulting products would be dependent on the size (or shape) of the attacking reagent.

Marshall and Carroll supported the above explanation by considering transition-state geometry.[153] These authors concluded that as the transition-state bond lengths increased (between carbonyl and attacking nucleophile, i.e., larger nucleophiles) in distance from the carbonyl, greater interactions with the 3,5-axial substituents would result, and therefore axial attack would decrease as the attacking species became bulkier.

In 1968, Cherest and Felkin ascribed the same steric interference to bond eclipsing factors[155] - "torsional strain" with respect to equatorial attack (eq. 27) and "steric strain" with the 3,5-axial substituents with respect


R
CH
$(CH_2)_2$
CH_2
C
H_e
O
H_a
H
M
Torsional Strain
R
H_e
O
H
M
H_a
R
OH
H_e
H
H_a

(27)


Steric Strain
M
H
R
CH
$(CH_2)_2$
CH_2
C
H_e
O
H_a
R
M
H
O
H_e
H_a
R
H
H_e
OH
H_a

(28)

to axial attack (eq. 28). The authors proposed that an important portion of the energy requirement for equatorial approach is due to torsional strain resulting from the development of two eclipsed nucleophile-hydrogen interactions with the pair of axial hydrogens at C-2 and C-6 early in the transition state.[142] Axial approach involves a much higher proportion of "classical" steric hindrance. In reactions of unhindered cyclohexanones with small nucleophiles, the "steric strain" associated with axial attack is expected to be smaller than the "torsional strain" associated with equatorial attack; therefore equatorial alcohol predominates (eq. 28). As the size of the nucleophile increases or as the 3,5-axial substituents become larger, the situation is reversed.

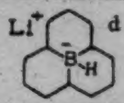
Recent investigations[156,157,159] have proved the "product development control" concept to be inoperable, and have supported the view[152,153,155] that the reduction stereochemistry is determined by a combination of steric interference, torsional strain, and electrostatic effects in the transition state.

Complex borohydrides[146-149, 163], boranes[164-166], aluminum hydrides[152,154,160,167], alkoxyaluminum dichlorides [168], and the use of Iridium-containing catalysts[169,170], are examples of reagents that effect stereoselective carbonyl reduction. Table VII gives the results for the reduction (under comparable reaction conditions) of a series of cyclic ketones by a number of these reducing reagents. The same cyclic ketones were investigated in the present study in order that comparisons could be made.

Two trends can be seen from the Table: (1) as the alkyl substituent becomes further removed from the carbonyl carbon the amount of equatorial attack (i.e., axial alcohol formation) decreases; and, (2) as the reducing reagent becomes larger, the stereoselectivity for axial alcohol formation increases.

TABLE VII

Reduction of Substituted Cyclic Ketones by Various Reducing Agents in THF at 0°C

Ketone	Alcohol Epimer	Epimer, %					
		$LiAlH_4$[a]	Disiamyl Borane[b]	$(IPC)_2BH$[b,c]	 [d]	Li(sec-Bu)$_3$BH[e]	IBOADC[f]
2-Methycyclopentanone	cis	21	78	94	94	98	--
2-Methylcyclohexanone	cis	25	79	94	97	99.3	98
3-Methylcyclohexanone	trans	16[d]	7.5	35	59	85	92
4-Methylcyclohexanone	cis	17[d]	12.5	33	52	80.5	90
4-*t*-Butylcyclohexanone	cis	8[g]	7.7	37	54	93	80-92
Camphor	exo	91	65	100	100	99.6	--

(a) H.C. Brown and H.R. Deck, *J. Amer. Chem. Soc.*, **87**, 5620 (1965).

(b) V.K. Varma, Ph. D. Thesis, Purdue University, Lafayette, Ind., 1967.

(c) Diisopinocampheylborane in diglyme at 0°C.

(d) H.C. Brown, and W.C. Dickason, *J. Amer. Chem. Soc.*, **92**, 709 (1970).

(e) H.C. Brown, and S. Krishnamurthy, *J. Amer. Chem. Soc.*, **94**, 7159 (1972)

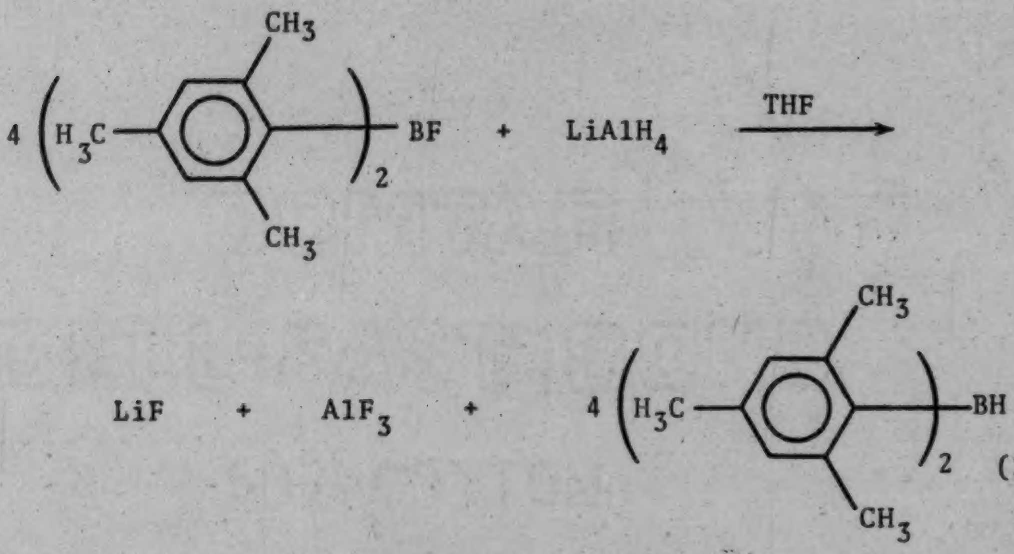
(f) Isobornyloxyaluminum dichloride, in ether; E.L. Eliel, and D. Nasipuri, *J. Org. Chem.*, **30**, 3089 (1965).

(g) P.T. Lansbury, and R.E. MacLeay, *J. Org. Chem.*, **28**, 1940 (1963).

During the course of the investigations with trimesitylboron, the possible preparation and use of the corresponding unknown dimesitylborane (DMB) became of interest. Subsequent studies on it and the corresponding lithium borohydride have led to a method superior to existing procedures for the reduction of unhindered cyclic ketones to the least stable alcohol by organoborohydride reducing agents.

RESULTS AND DISCUSSION

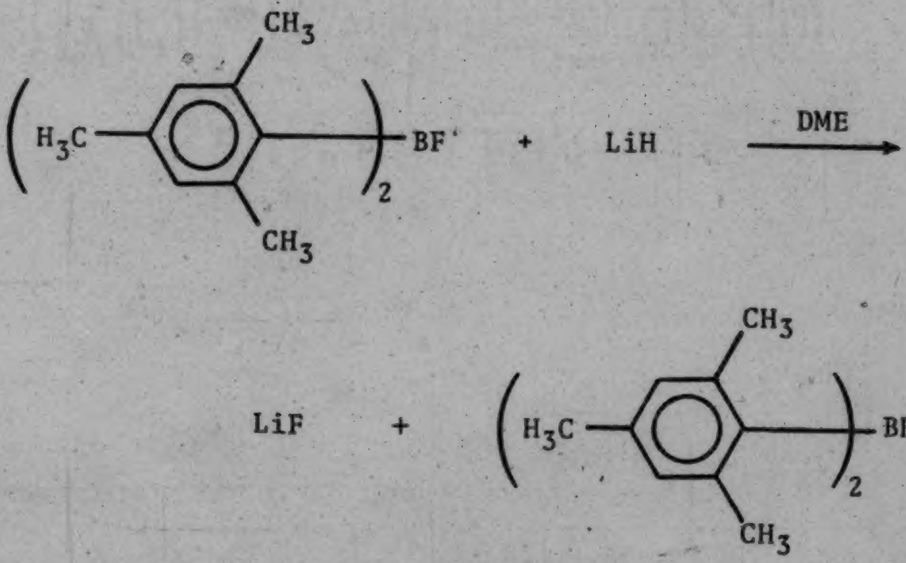
Dimesitylborane (DMB) was initially prepared by the addition of one equivalent of a standard ethereal lithium aluminum hydride solution[171] to four equivalents of dimesitylboron fluoride[6,172] (eq. 29). When the addition was performed at 0°C, a few hours of stirring were required before the DMB precipitated. When carried out at 25°C, the reaction was exothermic and the DMB precipitated within ten minutes: mp 166 - 168°C (sealed tube); mass spectrum: *m*/*e*: calcd for $C_{18}H_{23}B^{11}$, 250.1892. Found: 250.1889; ir (nujol): 1605(s), 1510(s) (B···H···B)[173] and 1435 cm^{-1} (s); ir (halooil): 1610(s), 1515(s) and 1440 cm^{-1}(s). However, various analyses of a number of preparations gave



(29)

poor and inconsistent analytical results (Found: C, 71.66 - 87.02; H, 7.76 - 9.51. Calcd: C, 86.44; H, 9.27) and furthermore, reductions of 2-methylcyclohexanone were not reproducible. This inconsistency is due to a number of factors, one of which presumably is the presence of various fluorides (eg. LiF, AlF_3) and hydrides ($LiMes_2BH_2$, $LiAlF_3H$, etc.) which are insoluble in THF and coprecipitate with the borane.

In order to circumvent these problems, the preparation was carried out with lithium hydride (eq. 30). Initial attempts to prepare the borane using diethyl ether or tetrahydrofuran as solvents at reflux temperatures and times ranging from 14 to 24 hours failed. However, the



(30)

preparation was successful when dimethoxyethane (DME) was employed as solvent.

This success is probably due to the ability of the "bidentate" DME molecule(s) to effectively coordinate in a claw-like fashion with the lithium cation.[212] This chelation is clearly demonstrated in the X-ray structure of the corresponding lithium "ate" complex, lithium dimesitylborohydride bis(dimethoxyethane) - see Figure 1.

Initial investigations using dimesitylborane were not concerned with isolating it in pure form, but rather involved a determination of its ability to stereoselectively reduce cyclic ketones and to do so with reproducibility. Thus no effort was made, initially, to separate the lithium fluoride which coprecipitated (eq. 30).

Employing this "crude" preparation, the reductions were performed with excellent reproducibility in the following manner. Lithium hydride (1.1 to 1.15 equiv.) was added to a solution of dimesitylboron fluoride (one equiv.) in DME under a nitrogen atmosphere. After refluxing for 20 - 24 hours, followed by cooling (the borane precipitated ca 20° below the reflux temperature) to 0°C, the cyclic ketone (one equiv.) was then added. The resulting heterogeneous mixture was stirred for 8 hours, and the intermediate organoboron species were oxidized by the addition of base (5% NaOH) and peroxide (30% H_2O_2). The aqueous phase was saturated with salt and the DME layer was analyzed by glc (see Experimental) for the isomeric alcohols (see Table VIII). Total yields for the least stable alcohol were >85%. The product alcohols (>80%) were easily isolated by elution with pet ether - ether (4 : 1) through a silica gel column. The by-product, 2,4,6-trimethylphenol, elutes first with pet ether.

3-Methylcyclohexanone, an unhindered ketone, afforded the corresponding trans-alcohol in 95% purity. Cis-4-methylcyclohexanol was obtained in 91% purity from 4-methylcyclohexanone. Similarly, 4-t-butylcyclohexanone reacted completely to produce the cis-carbinol (93%).

The results, particularly for the 3- and 4-substituted cyclohexanones, indicated that this crude mixture containing the borane showed excellent potential as a highly selective reducing reagent. In addition, when comparing this method to others[146-148, 163, 165, 166, 168] known to produce the less stable epimeric alcohol in high purity, one must take into account that the by-products of other methods (isoborneol[165, 166, 168] and aliphatic alcohols[146-148]) are highly volatile and therefore difficult to separate from the desired products. In contrast, the by-product in the present method is an easily separable phenol which can be removed by simple chromatographic techniques.

TABLE VIII

Reduction of Various Cyclic Ketones with DMB in DME at 0°C for 8 hours

Ketone[a]	Least Stable Epimer	% Least Stable Alcohol (Unreacted Ketone) pure DMB	% Least Stable Alcohol (Unreacted Ketone) DMB + 10-15% xs LiH
2-Methylcyclopentanone	cis	99.0 (47)	99.5 (10-15)
2-Methylcyclohexanone	cis	90 (38)	99 (8-9)
3-Methylcyclohexanone	trans	33 (4)	95 (0-5)
4-Methylcyclohexanone	cis	21 (0)	91 (0)
4-*t*-Butylcyclohexanone	cis	--	93 (0)
Camphor	exo	--	N.R. (100)

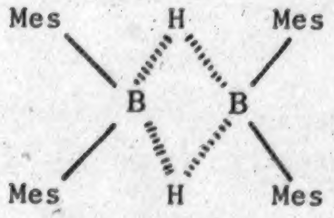
(a) Ratio of hydride to ketone was 1.2 : 1.0.

Attention was then turned to isolating pure dimesitylborane (free of lithium fluoride), characterizing it, and re-running the reductions of the various cyclic ketones with the pure sample.

Pure dimesitylborane was obtained in the following manner. After refluxing a mixture of lithium hydride (1.1 - 1.15 equiv.) and dimesitylboron fluoride (1.0 equiv.) in DME for 20 - 24 hours as before, anhydrous benzene was added to the hot mixture. The LiF precipitated, and was filtered from the hot DME-benzene solution. The filtrate was concentrated (to 50% of volume) by distillation under nitrogen. When additional benzene was added, no further precipitation resulted. The benzene was removed (by distillation) and the residue was recrystallized twice from anhydrous DME to afford a white crystalline solid; mp 163 - 166°C; ir (halooil): 1515 cm^{-1} (B···H···B bridge); mass spectrum: m/e: calcd for $C_{18}H_{23}B^{11}$: 250.1892. Found: 250.1886; molecular weight (osmometric) in benzene gave a value of 240. The nmr (benzene-d_6, 100 MHz) spectrum exhibited a singlet at δ 6.70 (4, ArH), a singlet at δ 2.27 (6, CH_3 at C_4) and a singlet at δ 2.20 (12, CH_3 at C_2 and C_6), and no evidence for B-H resonance in the nmr.

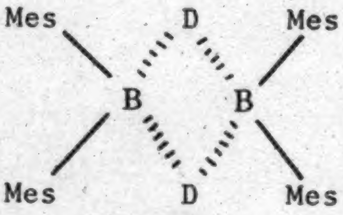
The infrared spectrum (nujol or halooil or benzene [1%] or cyclohexane [1%]) exhibited an absorption band at 1510 - 1515 cm^{-1} and no absorption due to an unassociated

B-H band at 2500 - 2600 cm^{-1} was observed.[175, 176] The corresponding deuterio analog[177] (from Mes$_2$BF and LiD), structure 17, showed absorption at 1118 cm^{-1} for the B···D···B stretch, a frequency shift in accord[175, 176] for the dimeric heavier isotope analog (Mes = mesityl).



1515 cm^{-1}

16



1118 cm^{-1}

17

Thus, this diarylborane, like the majority of dialkylboranes reported (e.g., disiamylborane[178], dicyclohexylborane[178], diisopinocampheylborane[178], and 9-borobicyclo[3.3.1]nonane (9-BBN)[179]) exists as a dimer.

Dimesitylborane is quite stable to air, much more so than the only other "stable" diorganoborane reported to date, 9-BBN.[179] In our hands, 9-BBN has on occasion spontaneously ignited or decomposed rapidly (liberating fumes) on exposure to air. DMB shows no such characteristics, even after prolonged exposure (no change in ir spectrum after 12 hr) to air or heat. The melting point of DMB (163 - 166°C) is the highest reported to date for diorganoboranes (9-BBN[179], mp 140 - 142°C; dicyclohexylborane[173], mp 103 - 105°C; disiamylborane[173], mp 40 - 44°C).

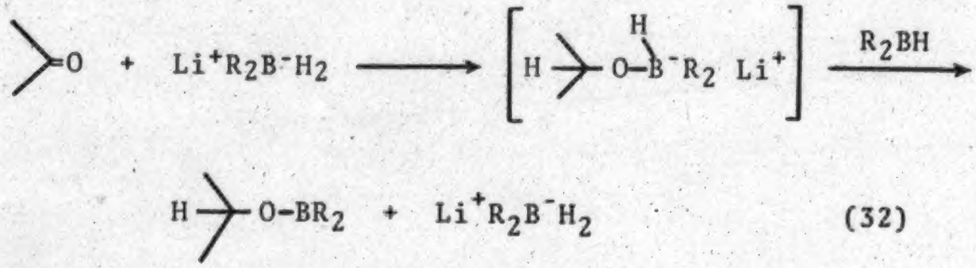
The reductions of methylcycloalkanones were repeated with pure dimesitylborane, under the same reaction conditions as before. Two major differences were observed (see Table VIII). One, the rate of reduction was slower, evidenced by the presence of large amounts of unreacted ketone. Two, the stereoselectivity decreased. In fact, this decrease was considerable in the 3- and 4-methylcyclohexanone reductions - from 95 to 33% and from 91 to 21%, respectively, of the corresponding least stable alcohols.

At first, it appeared possible that these differences might be due to the presence or absence of lithium fluoride (i.e., a Lewis acid). However, when the reductions were performed using pure DMB with lithium fluoride (0.5, 1.0 and 2.0 equiv.) added intentionally, the ratio of product alcohols were similar to those obtained with pure DMB.

The cause for the differences in results (Table VIII) has since been determined by Dr. S. Akiyama to be due to the presence of the 10 - 15% excess lithium hydride employed. This excess reacts with the DMB to form an "ate" complex of lithium dimesitylborohydride (eq. 31).

$$(Mes)_2BH + LiH \longrightarrow Li^+[(Mes)_2BH_2]^- \qquad (31)$$

Since the rate of reduction of a ketone with the borohydride is faster than that of a borane, a possible explanation of the results is illustrated by equation 32. Similar displacements of weaker Lewis acids from alkoxyborohydrides



(32)

by a stronger Lewis acid are documented.[180, 181] Thus, one view of the process is to regard the borohydride as a catalyst in the reduction. (Alternatively, one could postulate expulsion of lithium hydride from the intermediate alkoxyborohydride, followed by reduction of R_2BH by LiH to form $Li^+R_2B^-H_2$. This appears less attractive a possibility, because under similar experimental conditions (0°C), dimesitylborane does not react with LiH.)

There is no doubt, however, that it is the borohydride not the borane, which is the agent responsible for the high stereoselectivity observed. The borohydride, structure 18, was subsequently isolated, mp 129 - 131°C (sealed tube). Nmr spectroscopic and X-ray crystallographic (see Figure 1

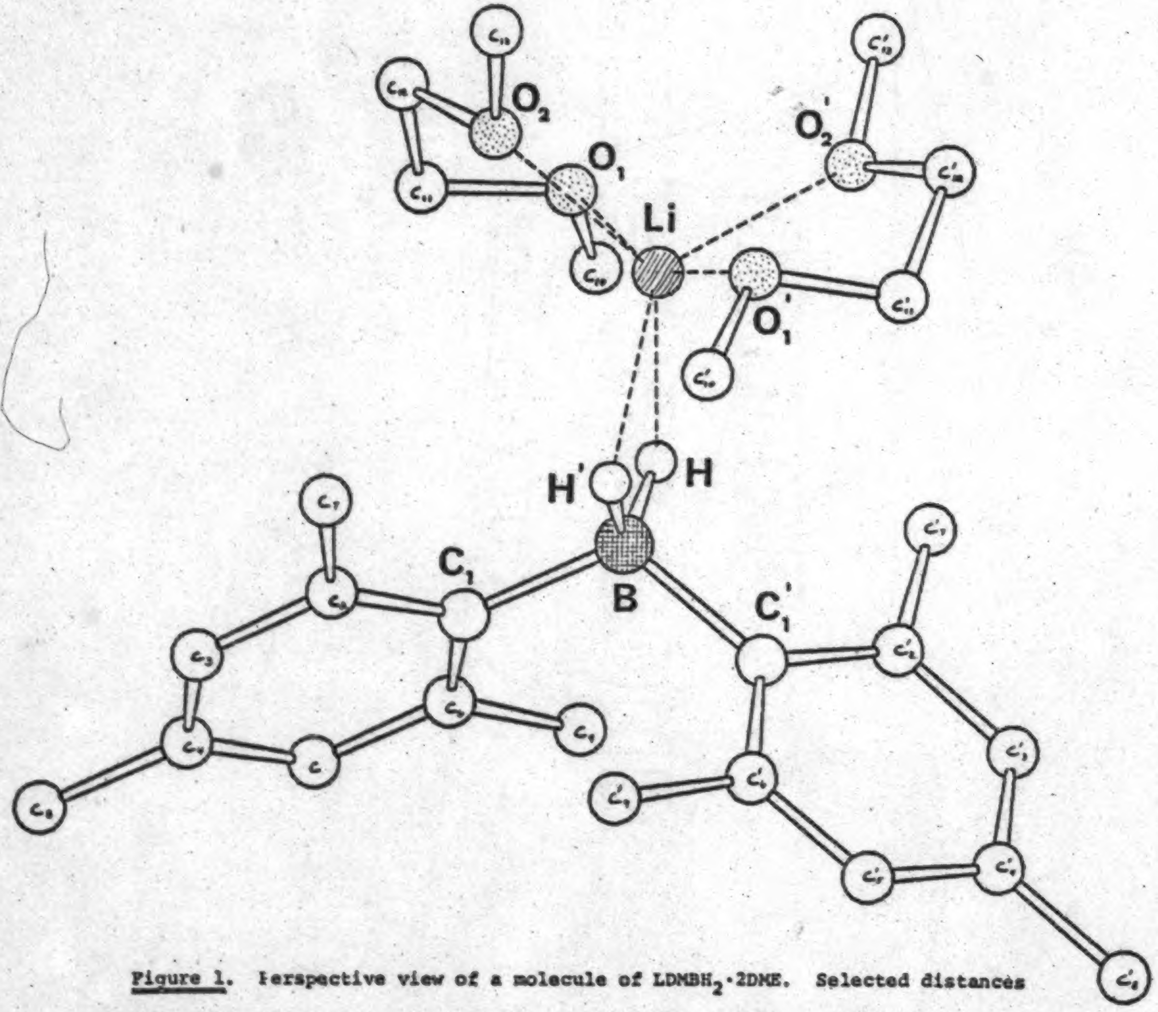


Figure 1. Perspective view of a molecule of LDMBH$_2$·2DME. Selected distances and angles (errors in parentheses): B-H 1.14(3), B-C(1), 1.640(5), B-Li 2.50(1), Li-H 2.06(4), Li-O(1) 2.353(4), Li-O(2) 2.000(7) Å and C(1)-B-C(1') 116.8(2), H-B-H' 110(3) deg.

TABLE IX^a

Selected Interatomic Distances and Angles from the X-ray Structure Determination of Lithium Dimesitylborohydride Bis(dimethoxyethane)

Bond Distances, Å^b

B - H	1.13 (3)	Li - H	2.05 (3)
B - C(1)	1.642(5)	Li - O(1)	2.353(4)
C(1) - C(2)	1.404(5)	Li - O(2)	1.999(7)
C(2) - C(3)	1.402(5)	C(10) - O(1)	1.404(6)
C(3) - C(4)	1.386(5)	O(1) - C(11)	1.390(8)
C(4) - C(5)	1.374(5)	C(11) - C(12)	1.494(9)
C(5) - C(6)	1.393(5)	C(12) - O(2)	1.439(7)
C(6) - C(1)	1.412(5)	O(2) - C(13)	1.387(6)
C(2) - C(7)	1.511(6)		
C(4) - C(8)	1.505(6)	C(11) - H(11A)	0.99(5)
C(6) - C(9)	1.495(6)	C(11) - H(11B)	0.96(7)
		C(12) - H(12A)	0.96(5)
C(3) - H(3)	1.01(4)	C(12) - H(12B)	1.16(7)
C(5) - H(5)	0.95(4)		
		C(3) - H(8B)	[illegible].80(4)
C(7) - H(7A)	0.92(3)	C(8) - H(8C)	0.93(4)
C(7) - H(7B)	0.90(3)	C(9) - H(9A)	0.86(3)
C(7) - H(7C)	0.92(3)	C(9) - H(9B)	0.83(3)
C(8) - H(8A)	0.98(4)	C(9) - H(9C)	0.99(3)

Other Distances, Å

B...Li	2.50(1)	O(1)....H	2.76(3)

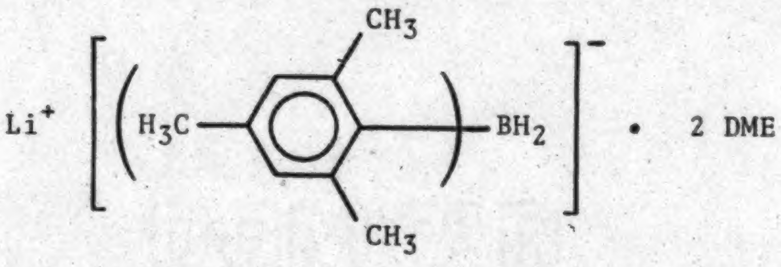
Angles, Deg.^{b}

C(1) - B - C(1')	116.9(4)	O(1) - Li - O(2)	76.9(2)
H - B - H'	108.0(3)	O(1) - Li - H	77.3(8)
C(1) - B - H	108.0(1)	O(1) - Li - O(1')	162.0(3)
C(1) - B - H'	108.0(1)	O(1) - Li - O(2')	92.3(2)
B - C(1) - C(2)	124.0(3)	H - Li - O(2)	131.7(9)
B - C(1) - C(5)	120.3(3)	H - Li - H'	53.0(1)
C(6) - C(1) - C(2)	115.6(3)	H - Li - O(1')	120.0(7)
C(1) - C(2) - C(3)	121.4(3)	H - Li - O(2')	110.5(8)
C(2) - C(3) - C(4)	122.2(4)	O(2) - Li - O(2')	110.9(3)
C(3) - C(4) - C(5)	116.6(4)	C(10) - O(1) - C(11)	112.3(5)
C(4) - C(5) - C(6)	122.6(4)	O(1) - C(11) - C(12)	108.3(5)
C(5) - C(6) - C(1)	121.5(4)	C(11) - C(12) - O(2)	108.9(6)
C(1) - C(2) - C(7)	122.6(3)	C(12) - O(2) - C(13)	111.6(5)
C(3) - C(2) - C(7)	116.0(4)	O(1) - C(11) - H(11A)	113.0(3)
C(3) - C(4) - C(3)	121.1(3)	O(1) - C(11) - H(11B)	102.0(4)
C(5) - C(4) - C(8)	122.3(4)	H(11A) - C(11) - H(11B)	119.0(5)
C(5) - C(6) - C(8)	117.3(3)	C(12) - C(11) - H(11A)	103.0(3)
C(1) - C(6) - C(8)	121.2(3)	C(12) - C(11) - H(11B)	111.0(4)
C(2) - C(3) - H(3)	119.0(2)	C(11) - C(12) - H(12A)	108.0(3)
C(4) - C(3) - H(3)	119.0(2)	C(11) - C(12) - H(12B)	113.0(4)
C(4) - C(5) - H(5)	122.0(2)	H(12A) - C(12) - H(12B)	122.0(4)
C(6) - C(5) - H(5)	116.0(2)	O(2) - C(12) - H(12A)	99.0(3)
B - H - Li	100.0(2)	O(2) - C(12) - H(12B)	103.0(3)

(a) X-ray measurements determined by Dr. R.M. Tuggle.

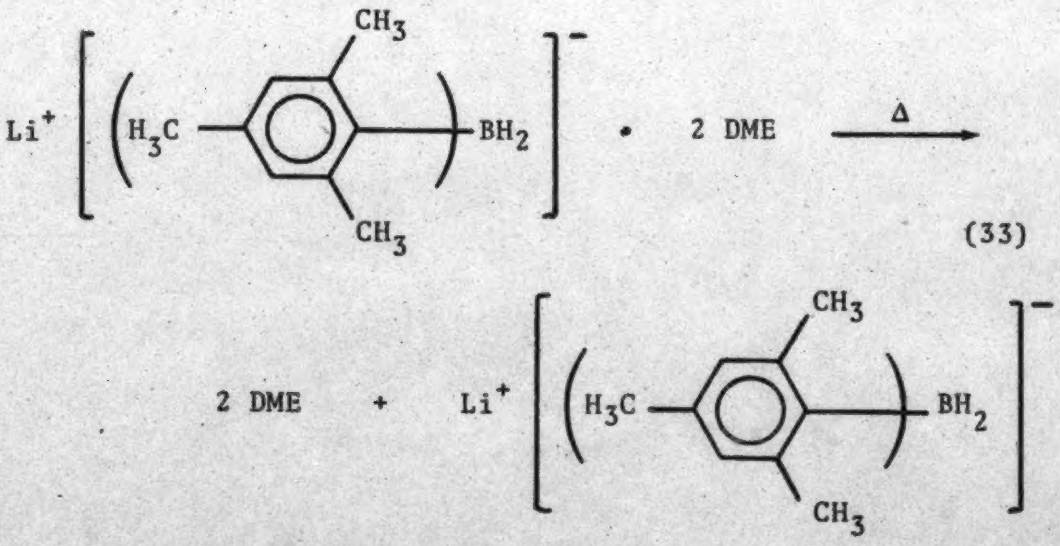
(b) Errors in parentheses.

and Table IX) studies showed that two molecules of dimethoxyethane (DME) were complexed with the lithium cation of the lithium borohydride.



18

Also, the new "ate" complex lithium dimesitylborohydride, mp 268 - 270°C (sealed tube), could be obtained free of the dimethoxyethane by heating and evacuating (130 - 155°C/0.08 mm) neat samples of $Li^+Mes_2B^-H_2 \cdot 2DME$, 18, for ca 4.5 hr (eq. 33).



(33)

Reductions of the cyclic ketones with $LiMes_2BH_2 \cdot 2DME$, $\underline{\underline{18}}$, show selectivity similar or greater to that first observed, but the reductions are complete in much shorter times (see Table X). Thus, reductions of 3- and 4-methylcyclohexanones afforded the corresponding axial-OH isomers in 99 and 94% isomeric purity, respectively, in essentially quantitative yield at 0° in 3 hr. Selectivities of this magnitude are apparently unprecedented for di- or triorganoborohydride reducing agents.

Subsequently, it was discovered that the procedures for isolating the product alcohols could be further simplified. Thus, by adding a small amount of water (instead of base and peroxide), followed by drying, evaporation of the solvent, and vacuum distillation from the by-product, dimesitylborinic acid, the product alcohols were easily obtained in $>$80% isolated yields.

In addition to the exceptional stereoselectivity observed, a noteworthy feature was the rate response of $\underline{\underline{18}}$ to ketones of differing structural environments. Although unhindered or moderately hindered cyclohexanones were completely reduced in three hours at 0°C, a highly hindered substrate, camphor, was totally inert to the reagent after eight hours at 0°C. Approximately three days at 25°C were required for complete reduction (99.8% exo), Table X.

In striking comparison, carbonyl reductions with bulky

TABLE X

Reduction[a] of Various Cyclic Ketones with Li $Mes_2BH_2 \cdot 2DME$ in DME at 0°

Ketone[b]	Least Stable Epimer	% Least Stable Alcohol[c]
2-Methylcyclopentanone	cis	98
2-Methylcyclohexanone	cis	99
3-Methylcyclohexanone	trans	99
4-Methylcyclohexanone	cis	94
4-*t*-Butylcyclohexanone	cis	94
Camphor	exo	99.8[d]

(a) Performed by Dr. S. Akiyama.

(b) Ratio of hydride to ketone was 1.3 : 1.

(c) Reaction time, 3 hours.

(d) At 25°, 72 hours.

triorganoborohydrides, although highly stereoselective, are rather rate-insensitive to structure and generally proceed at remarkably rapid rates even for ketones with widely different steric surroundings. For example, both 4-methylcyclohexanone and camphor are completely reduced by Li^+(sec-Bu)$_3$$^-$BH in one hour at 0°C[186] (see Table VII).

In conclusion, this new reagent, 18, is so consistent in its attack from the less hindered side of the carbonyl group that it may find use as an important tool for determining the steric environment of particular carbonyl groups. In addition, it may find use in regiospecific mono-reductions of appropriate complex di- or polycarbonyl substrates in unprotected form.

EXPERIMENTAL

General Considerations

Infrared (ir) spectra were recorded using a Perkin-Elmer 421 G or Unicam SP 1000 Infrared Spectrophotometer.

Mass Spectra were recorded on an AEI Model MS-2 or Model MS-9 Spectrometer.

Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 or HA-100 Spectrometer in the indicated solvents with tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in δ values relative to TMS=0. The following abbreviations were used in the text: bd = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

Melting points were determined using a Reichert or Buchi melting point apparatus and are uncorrected.

Gas chromatographic (glc) analyses were performed using a Perkin-Elmer Model 900 Capillary Gas Chromatograph with a 150 ft. x 0.010 in. β,β-oxydipropionitrile capillary column (Column A), a Hewlett Packard 402 High Efficiency Gas Chromatograph with an 18 ft. x 1/4 in. glass column of 10% DEGS on 60/80 Chromosorb P AW (Column B), a Varian Aerograph Series 1200 or Series 1400 Chromatograph with a 5 ft. x 1/8 in. 20% DEGS on 60/80

Chromosorb W (Column C) and an Aerograph A90 -P3 with a 10 ft. x 1/4 in. 20% Carbowax 20 M on 60/80 Chromosorb W (Column D).

Microanalyses were performed by the Microanalytical Laboratory, University of Alberta.

All reductions were performed under a dry nitrogen atmosphere. Tetrahydrofuran (THF) and dimethoxyethane (DME) were freshly distilled from lithium aluminum hydride under nitrogen before use. All (liquid) ketones used in these reductions were also distilled before use; 4-t-butylcyclohexanone was recrystallized from pentane, mp 46 - 49°C. Boron trifluoride etherate was purified by vacuum distillation from calcium hydride. Lithium hydride, from Alfa Inorganics, was used as received. In several runs using older exposed samples, either prolonged reaction periods were necessary or the reaction was entirely unsuccessful.

Column chromatography was performed using Kiesel Gel Silica Gel M of 0.15 - 0.30 mm granulation as adsorbent.

Preparation of Dimesitylboron fluoride[6, 172]

A one litre three neck round bottom flask fitted with a mechanical stirrer, a pressure equalizing dropping funnel (250 ml), an efficient condenser and attached to a nitrogen source, was flame dried under a flow of nitrogen. The flask also contained magnesium turnings (14.1 g, 0.58 g-at.). Anhydrous THF (70 ml) was added to the cooled flask. The dropping funnel was charged with 2-bromomesitylene[182] (100 g, 0.50 mole). Approximately 5 ml of the halide was then added to initiate the reaction (on occasion, gentle heating was necessary). The remainder of the halide was diluted with THF (30 ml) and anhydrous diethyl ether (150 ml). Additional diethyl ether (100 ml) was added to the reaction vessel once the reaction was initiated. The halide solution was then added dropwise so as to maintain a vigorous reflux. After complete addition of the halide, the solution was refluxed for a further four hours and left standing overnight.

Boron trifluoride etherate (33.4 g, 0.235 mole) in diethyl ether (150 ml) was then added dropwise (30 minutes) to the Grignard reagent. The addition causes gentle refluxing of the ether. After total addition, the mixture was stirred under gentle reflux for 1.5 hours.

The resultant clear light yellow supernatant was then concentrated under nitrogen, and the residue was short path vacuum distilled to provide 46 g (73% yield) of a clear colourless liquid, dimesitylboron fluoride, which solidified on cooling; bp 126 - 130°C/0.15 mm .

Numerous repetitions of the above procedure provided dimesitylboron fluoride in yields varying between 69 and 76%.

Preparation of Dimesitylborane by Reaction of Dimesitylboron Fluoride.

With Lithium Aluminum Hydride

A solution containing 5.0 ml of a standard 1.7M $LiAlH_4$ solution[171] (8.51 mmole, 1.0 equiv.) and THF (10 ml) was added dropwise (4 min.) to a solution of dimesitylboron fluoride (8.4 g, 31.3 mmole, 3.68 equiv.) in THF (50 ml) at 0°C. After total addition, the solution was allowed to warm to room temperature. A white crystalline precipitate resulted after an additional four hours of stirring. The mother liquor was decanted, and the precipitate was washed successively with anhydrous THF, Skelly "B" and THF, then dried (under a stream of argon), mp 166 - 168°C (sealed tube); mass spectrum: m/e: 250 (M^+); ir (halooil): 1515 cm^{-1} (s, bd) (B···H···B); nmr ($CDCl_3$): δ 6.71 (m, 4, ArH), 2.23 (s, 6, $-CH_3$ at C_4) and 2.02 (s, 12, $-CH_3$ at C_2 and C_6). A Beilstein test showed a green flame (indicative of the presence of boron). Treatment of a small portion of the solid with ethanol resulted in evolution of a gas and formation of ethyl dimesitylborinate, mp 58 - 59.5°C (from abs. C_2H_5OH): mass spectrum: m/e: calcd for $C_{20}H_{27}OB^{11}$, 294.2155. Found: 294.2161. Nmr ($CDCl_3$): δ 6.69 (s, 4, ArH), 3.99 (q, 2, $-O-CH_2-$), 2.22 (s, 18, $Ar-CH_3$) and 1.27 (t, 3, $-CH_2-CH_3$); ir($CHCl_3$): 1608(s), 1370(s) (-B-O), 1315(s), 882 and 845 cm^{-1}.

However, elemental analysis of the precipitate gave poor results: Calcd for $C_{18}H_{23}B$: C, 86.44; H, 9.27. Found: C, 71.66; H, 7.76. (Other samples prepared in a similar manner likewise gave poor analyses.)

This crude borane was shown to reduce cyclohexanone to cyclohexanol quantitatively at 25°C in one hour (50% conversion at 0°C for one hour). When the reduction was extended to 2-methylcyclohexanone, inconsistent results were noted, varying from 80 - 95% cis and 5 - 20% trans.

With Lithium Hydride

Initial attempts to bring about reaction between dimesitylboron fluoride and LiH in refluxing diethyl ether (24 hr) and refluxing THF (14 to 20 hr) met with no success. However, when DME was employed as solvent, reaction occurred resulting in excellent yields of dimesitylborane.

The simplest manner of using the borane (or the corresponding borohydride) is to prepare and utilize it in situ, thus avoiding the isolation step. The presence of LiF does not interfere.

General Reduction Procedure for Reactions Involving the "Crude" Dimesitylborane.

To 4.10 - 4.15 g (15.3 - 15.4 mmole) of dimesitylboron fluoride in dry DME (50 ml) in a 100 ml three neck flask equipped with a condenser, stirring bar, and a nitrogen inlet tube was added 0.132 to 0.140 g (16.5 - 17.5 mmole, 1.10 to 1.15 equiv.) of lithium hydride. The mixture was heated (under a nitrogen atmosphere) to reflux for 20 - 24 hours. After cooling to 0°C (the borane precipitates) a solution of the ketone (12.0 - 13.2 mmole) in dry DME (10 ml) was added to the heterogeneous mixture all at once and the mixture was stirred at 0°C for 8 hours. At this point, the reaction mixture appears as a milky suspension.

To this mixture was then added at 0°C 15 ml of 5% NaOH solution and 30% H_2O_2 (5 ml). The resulting mixture was warmed to 40 - 50°C (one hour), with rapid stirring, then washed with a saturated K_2CO_3 solution (two 25 ml portions). The combined aqueous extract was washed with ether (two 20 ml portions). The organic extracts were combined, and washed with brine (60 ml), dried (Na_2SO_4), evaporated. The residue was made up to 25 ml in a standard flask with DME.

This solution was then analyzed by glc for determination of the relative amounts of epimeric alcohols. For all reductions except that of 4-_t_-butylcyclohexanone, column A was employed at a column temp. of 80°C (inj. temp. 110 - 120°C, det. temp. 100 - 110°C). For analysis of the 4-_t_-butylcyclohexanone reduction, column B was employed at column temp. of 140°C (inj. temp. 145°C, det. temp. 160°C;

gas flow rates: H_2, 40 ml/min; O_2, 150 ml/min; He, 70 ml/min). Results are given in Table VIII. All reductions were performed at least twice, with excellent reproducibility.

Absolute yields (glc) were determined by using column C at 110 - 115°C, and indicated that the reactions were quantitative.

Isolation of the product alcohols involved evaporation of the solvent, followed by column chromatography on silica gel of the resultant residue. Elution with Skelly "B" gave 2,4,6-trimethylphenol (mesitol); elution with Skelly "B" - ether (7 : 3) gave the alcohol. Isolated yields were >80%.

The isolated synthetic samples of cis-2-methylcyclohexanol and cis-4-t-butylcyclohexanol exhibited identical ir absorptions and glc retention times as those of authentic samples. Authentic samples of trans-3-methyl- and cis-4-methylcyclohexanol were not available. However, the isolated synthetic materials possessed properties in accord with literature data (see following procedures).

A typical experiment is described below.

Reduction of 3-Methylcyclohexanone

To the crude borane mixture [formed by reaction of dimesitylboron fluoride (4.107 g, 15.3 mmole) with lithium hydride (0.137 g, 17.2 mmole) as described above in the general procedure] at 0°C, a solution of 3-methylcyclohexanone (1.477 g, 13.17 mmole) in DME (10 ml) was added all at once. After 8 hrs. at 0°C the reaction mixture was oxidized by the addition of 5% NaOH solution (15 ml) and 30% H_2O_2 solution (5 ml) followed by stirring for one hour at 40 - 50°C. The mixture was worked up as above. Glc (column A) analysis indicated 95 and 5% formation of the trans- and cis-3-methylcyclohexanols, respectively. *

The solvent was evaporated and the residue was chromatographed on silica gel. Elution with Skelly "B" gave 2,4,6-trimethylphenol; mp 70 - 72°C (from Skelly "B") [lit[183] 72°C]; nmr ($CDCl_3$); δ 6.78 (s, 2, Ar$\underline{H}$), 4.50 (s, 1, -O$\underline{H}$), and 2.17 (s, 9, -C$\underline{H}_3$); ir ($CHCl_3$): 3600 (phenolic -OH) and 855 cm^{-1} (1,2,3,5-aromatic); mass spectrum: m/e: 136 (M^+). Further elution with Skelly "B" - ether (7 : 3) gave a clear liquid (1.48 g) which, upon vacuum distillation, afforded trans-3-methylcyclohexanol

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* As a confirmation for the assignment of the cis/trans peaks by glc, 3-methylcyclohexanone was reduced by $LiAlH_4$ in THF as previously reported[163] - a procedure which is known to produce predominantly the cis-alcohol. Glc (column A, 80°C) indicated a 17 : 83 trans : cis ratio in agreement to that reported (16 : 84), thereby confirming our assignments.

(0.98 g), bp 103 - 105°C/68 mm [lit[184] 78 - 79°C/20 mm; [185] 64 - 65°C/11 mm]; ir (liquid film): 1140, 995, and 945 cm^{-1} (identical to values reported[186] for the 3-*trans*-epimer: 1140, 995 and 943 cm^{-1}; the 3-*cis*-epimer gives 1100, 1070 and 1023 cm^{-1} absorption bands[186]).

As additional proof of structure, the *p*-nitrobenzoate derivative was prepared as described in Shriner, Fuson and Curtin[187], mp 61 - 62°C (from methanol) [lit[186] 61.5 - 62.5°C, [188] 60 - 61°C].

Reduction of 4-Methylcyclohexanone

Reduction of this ketone, using the identical procedure described above, afforded *cis*-4-methylcyclohexanol (91% epimeric purity), bp 115 - 119°C/70 mm [lit[184] 173 - 174°C/750 mm, [184] 78 - 79°C/20 mm]; ir (liquid film): 1150, 1075, 1030, 985 and 925 cm^{-1} (in agreement with values reported [186]; for the *cis*-4-alcohol: 1145, 1075, 1035, 985 and 925 cm^{-1}; for the *trans*-4-alcohol: 1090, 1050 and 1010 cm^{-1}); *p*-nitrobenzoate derivative; mp 93 - 95°C (from Skelly "B") [lit[186] 95 - 96°C].

Reduction of Camphor

Under the conditions described above, no reduction occurred. The ketone was recovered in 97% yield.

Isolation of Pure Dimesithylborane

To 34.5 g (0.13 ml) of dimesitylboron fluoride in a 500 ml three neck flask equipped with a magnetic stirring bar, a condenser and a nitrogen inlet tube was added anhydrous DME (250 ml) and lithium hydride (1.184 g, 0.149 mmole). The mixture was refluxed for 24 hours at which point benzene (50 ml) was added. A white solid (LiF) precipitated. The clear supernatant (while hot) was then decanted from the white precipitate.

The solution was concentrated by distillation and dry DME (80 ml) was added. The resulting solution was brought to reflux, then cooled slowly to crystallize the DME. Once crystallized, the solvent (DME) was decanted from the borane (DME). The solid was crystallized once again using this procedure (from DME). Decantation of the solvent, followed by drying under vacuum (0.15 mm), afforded 16.5 g (51.3% yield) of pure dimesitylborane; mp 163 - 166°C (sealed tube); Anal. Calcd for $C_{18}H_{23}B$: C, 86.71; H, 9.37; Found: C, 86.44; H, 9.27; mass spectrum: $\underline{m}/\underline{e}$: calcd for $C_{18}H_{23}B^{11}$: 250.1892; Found: 250.1886; nmr (benzene-d_6, 100 MHz): δ 6.70 (s, 4, Ar$\underline{H}$), 2.27 (s, 6, -C$\underline{H}_3$ at C_4), 2.20 (s, 12, -C$\underline{H}_3$ at C_2 and C_6), resonance for the B-$\underline{H}$ could not be detected.

The ir spectrum (nujol, halooil, 1% benzene, or

1% cyclohexane) exhibited an absorption band at 1510 - 1515 cm^{-1}. No absorption for an unassociated B-H band at 2500 - 2600 cm^{-1} was ever observed.[175, 176] The corresponding deuterio analog (mass spectrum: m/e: calcd for $C_{18}H_{22}DB^{11}$: 251.1956; found: 251.1951), prepared in a similar manner[177] (from the boron fluoride and LiD) showed ir absorption at 1118 cm^{-1} (B···D···B).[175, 176]

A molecular weight determination (osometric) of pure DMB in benzene gave a value of 240.

The pure DMB obtained from the above procedure was then used in a set of four reductions (substrates and results are listed in Table VIII).

General Reduction Procedure for Reactions Using the Isolated Dimesitylborane

To 3.0 - 3.3 g (12 to 13.0 mmole) of dimesitylborane in a 100 ml three neck flask equipped with a magnetic stirring bar and gas inlet and outlet tubes was added anhydrous DME (50 ml). The heterogeneous mixture was cooled to 0°C and the ketone (10 mmole) in DME (10 ml) was added all at once. The mixture was kept at 0°C for 8 hrs. then treated, at 0°C, with 5% NaOH solution (15 ml) and 30% H_2O_2 solution (5 ml). The resulting mixture was then heated for one hour at 40 - 50°C, with stirring. Brine (25 ml) was added and the aqueous extract was washed with ether (two 20 ml portions). The combined organic extract was washed with brine (60 ml), dried (Na_2SO_4), evaporated and made up to 25 ml (with DME) in a standard flask for analysis by glc.

Reductions of 4-Methylcyclohexanone with Dimesitylborane and Added Lithium Fluoride.

The reduction procedure was identical to that described directly above, with the exception that after LiF was added, the resulting mixture was stirred for 30 minutes at room temperature before cooling to 0°C.

Three reductions of 4-methylcyclohexanone were performed using 2.0 equiv., 0.5 equiv. and no equiv. (i.e., a blank) of added lithium fluoride. All gave identical results i.e., 45% of cis-carbinol (glc, column A).

Similar results (i.e, identical ratio of epimers) were obtained in the reductions of both 3- and 4-methylcyclohexanones when the reactions were performed in the absence or presence of added LiF (1 equiv.).

Preparation of Lithium Dimesitylborohydride Bisdimethoxyethane.[189]

A mixture of dimesitylborane (22.0 g, 88 mmole) and lithium hydride (0.698 g, 88 mmole) in DME (270 ml) was refluxed for 2 hours. After the resulting solution was decanted through glass wool to remove unreacted lithium hydride, it was concentrated to ca 180 ml. The deposited crystals were separated from the mother liquor by decantation, washed with dry pentane, and dried under reduced pressure (0.5 mm Hg) at room temperature (12 hr). The crystals (33.4 g, 87%) melted at 129 - 131°C in a sealed tube: ir (nujol): 2180, 2200 and 2280 (v.s.); ($CHCl_3$) 2120; (benzene) 2100; (THF) 2180 cm^{-1} (-BH); mass spectrum: m/e: 250 (R_2BH) and 90 (DME), no 438 peak. Anal. Calcd. for $C_{26}H_{44}O_4BLi$: C, 71.24; H, 10.12; B, 2.47; MW 438. Found: C, 71.21; H, 9.88; B, 2.35; MW 421 (benzene), 213 (chloroform). Nmr ($CDCl_3$, 100 MHz): δ 6.60 (s, 4, ArH), 3.46 (s, 8, $-(CH_2)_2-$), 3.29 (s, 12, $-OCH_3$), 2.24 (s, 12, $-CH_3$ at C_2 and C_6) and 2.19 (s, 6, $-CH_3$ at C_4).

The Reduction of Ketones with Lithium Dimesitylborohydride Bisdimethoxyethane.

The following procedure is representative. A dry 100 ml three meck round bottom flask kept under nitrogen was charged with 3.3 g (13 mmole) of dimesitylborane, 0.103 g (13 mmole) of lithium hydride, and 50 ml of dry DME. The mixture was refluxed (30 min.) until a homogeneous solution was obtained. To the mixture, at 0°C, was added 10 mmole of 3-methylcyclohexanone in DME (10 ml). The reaction mixture was stirred for 3 hours, then treated, at 0°C, with 5% NaOH solution (15 ml) and 30% H_2O_2 solution (5 ml), followed by warming to 40 - 50°C for one hour. The yield of the alcohols was determined (glc, column A at 80°C) to be 99.5% cis and 0.5% trans-3-methylcyclohexanol.

Isolation of the product alcohol can be performed as described previously, employing a column of silica gel. As an alternative isolation procedure, the following is described. Instead of treating the crude borohydride reduction mixture with base and peroxide, water (15 ml) alone can be used. After extraction, drying(Na_2SO_4), and evaporation of the solvent, the product alcohol can be distilled directly. Using this procedure, the reduction of 3-methylcyclohexanone gave an 82% isolated yield of trans-3-methylcyclohexanone, bp 70 - 71°C/11 mm. The distillation residue was crystalline dimesitylborinic acid (98%), mp 141 - 142°C (from Skelly "B") [lit^6 140 - 141°C, ^{172} 142°C].

Results for the reductions of the other ketones are given in Table X. In all cases, the reductions were complete with no residual ketones detected.

Preparation of Lithium Dimesitylborohydride free of Dimethoxyethane.

A sample (3.9 g) of lithium dimesitylborohydride bis(dimethoxyethane) was placed in vacuo (0.08 mm Hg) at 130°C for 3 hr; then at 155°C for 1.5 hr. The trapped liquid was identified as DME by comparison of the ir spectrum with that of an authentic sample. The white powder obtained (2.2 g, 96%) in this manner exhibited: mp 268 - 270°C (sealed tube); ir (nujol): 2140 cm^{-1} (B-H); ($CHCl_3$): 2140 cm^{-1} (B-H); mass spectrum: $\underline{m}/\underline{e}$: 250 ($R_2BH$), no 258 258 ($M^+$) peak; nmr (THF-$d_8$, 100 MHz): δ 6.48 (s, 4, Ar$\underline{H}$), 2.24 (s, 12, -C$\underline{H}_3$ at C_2 and C_6) and 2.12 (s, 6, -C$\underline{H}_3$ at C_4). Anal. Calcd. for $C_{18}H_{24}BLi$: C, 83.75; H, 9.37; B, 4.19; MW 258. Found: C, 83.46; H, 9.09; B, 3.90; MW (chloroform) 248.

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